Risk factors for Type 2 Diabetes Mellitus: Metabolic Syndrome, Insulin Resistance and Primary Prevention.

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Abstract

Aims:

The purpose of the study was to identify the extent of metabolic syndrome on the basis of ATP III and IDF definition in subjects aged 25 years and above from an urban population of Karachi. Also to see the association of risk factors related to diabetes and metabolic syndrome in this population. And finally to prove the hypothesis of intervention effect on the onset of type 2 diabetes in a high risk urban population and evaluate the rate of conversion of IGT to diabetes by these interventions in this population.

Methods:

The epidemiological survey was designed to see the prevalence of metabolic syndrome and its risk factors among 500 randomly selected households in Lyari, an urban area within Karachi city in 2004 . We generated a computerized random sample of the households from among the 85,520 households in Lyari Town. There were 11 union councils in Lyari Town where the samples were taken and each union council had equal opportunity to be represented in the sample selection. We expected approximately 1000 adult men and women 25 years and above in the households selected in Lyari Town. If members of a household that had been selected refused to consent to household interviews, we knocked on the third door to the right of that house and seeked consent there. Out of the 85,520 households, 532 households were randomly selected and 867 adults ≥25 years old consented to take part in the survey; 363 of these subjects gave blood samples.

The second study was a primary prevention trial which was started in the city of Karachi in 2006. It was a prospective randomized clinical trial (RCT) to assess the effect of intervention for 18 months on high risk subjects. Nearly 2000 suspected high risk cases identified by a questionnaire were to be invited to participate. Considering 30% IGT cases in high risk individuals around 600 were expected to have IGT based on OGTT. The IGT cases were then randomly allocated on three different arms, two preventive groups and one control group, all with 200 participants (one of the preventive arms included metformin 500mg twice daily). An estimated 5000 people attended the diabetes prevention lectures and visited the screening camps and around 2300 people filled in the high risk questionnaire only 1825 were identified as high risk. Of these 1739 high risk subjects undertook a standardized oral glucose tolerance test (OGTT) and 317 subjects were identified as having impaired glucose tolerance (IGT group) and were randomized into the three groups.

Results:

The prevalence of diabetes was 9.4%, whereas 5.6% had impaired fasting glucose (abnormal glucose tolerance 15%). The prevalence of metabolic syndrome according to the IDF definition and modified ATP III criteria was 34.8% and 49%, respectively. Inclusion of modified waist circumference and specific body mass index (BMI) cut offs for Asians might have helped in this increased prevalence of the metabolic syndrome.

Dietary data about specific food items was available for 867 adults. Participants also completed a health and lifestyle questionnaire and 363 subjects provided fasting blood samples for glucose and lipids. Dietary intake was assessed by a questionnaire to identify consumption of 33 specific food items and the dietary patterns categorized into 6 food groups was assessed by cluster analysis. Five dietary patterns were identified through cluster analysis. Cluster 1 had the lowest proportion of persons with metabolic syndrome i.e. 42.7% while cluster 2 had the highest percentage of metabolic syndrome subjects (56.3%) ($p=0.09$). Consumption of fat and calorie dense foods was significantly higher among highest risk group (cluster 2) compared to lowest risk group (cluster 1) ($p = 0.0001$). The consumption of food groups containing fruit, milk and meat was also more than twice in high risk compared to low risk group ($p = 0.0001$). Even within the same population there are marked differences in dietary patterns and these apparently contribute to the risk of developing metabolic syndrome.

Insulin Resistance (IR) was defined at 75th percentile cut off of insulin levels (9.25 U/mL) and HOMA-IR (1.82). The 25th percentile cut off was used for defining IR in QUICKI (0.347) and McAuley Index (6.77).

In the second study which was the primary prevention trial 273 subjects out of 317 subjects completed the study giving a compliance rate of 86%. A total of 47 incident cases of diabetes were diagnosed during the study. The overall incidence of diabetes was 4 cases per 1000 person-months with the incidence of diabetes as 8.6 cases in the control group, 2.5 cases in the Life Style Modification (LSM) group and 2.3 cases per 1000 person-months in the LSM+drug group.

Conclusion:

In the first study we observed high prevalence of metabolic syndrome irrespective of the definition applied in this urban population. This may call for immediate action such as preventive measures to halt the accelerating risk of diabetes and CVD which is leading to a possible unparalleled rise in the cost of health care and human suffering.

To initiate a preventive program we need to make dietary changes within the population and we found marked differences in dietary patterns which were apparently contribute to the risk of developing metabolic syndrome in the same population. Dietary pattern studies will help elucidate links between diet and disease and contribute to developing healthy eating guidelines.

A common approach towards managing subjects with metabolic risk factors which could help physicians would be able to identify IR cases earlier and defining IR reference values identified from simple indirect methods would be of value in such cases. However larger population based studies are needed to further define and validate the cutoff values defined for insulin resistance in our population.

The primary prevention study was initiated after we had some baseline information from our first epidemiological study and it showed that lifestyle intervention had a major impact in preventing diabetes among IGT subjects in this region. However, addition of drug in the intervention did not show any improved results. Resource constrain societies are challenged with the additional burden of diabetes cost on their already ailing economy and such lifestyle intervention approach would be of benefit in such communities. Therefore, we recommend that lifestyle modification advice and follow-up should be incorporated in primary health care.

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List of Acronyms

ADA	American diabetes association
AACE	American Association of Clinical Endocrinology
BMI	Body mass index
CHOD-PAP	Cholesterol Oxidase – Para amino phenazone
CHD	Coronary Heart Disease
CVD	Cardiovascular Disease
EGIR	European Group for the Study of Insulin Resistance
GOD-PAP	Glucose Oxidase – Para amino phenazone
GPO-PAP	Glycerol Phosphate Oxidase –Para amino phenazone
HOMA	Homeostasis model assessment
IDF	International Diabetes Federation
LDL	Low density lipoprotein
MS	Metabolic Syndrome
NCEP – ATP III	National Cholesterol Education Program : Adult Treatment Panel
HDL	High density lipoprotein
TGs	Triglycerides
T2DM	Type 2 Diabetes Mellitus
WHO	World Health Organization

List of Papers

1. **Paper 1**

Prevalence of Metabolic Syndrome in Urban Pakistan (Karachi): Comparison of Newly Proposed International Diabetes Federation and Modified Adult Treatment Panel III Criteria.

M. Zafar Iqbal Hydrie, A. Samad Shera, Asher Fawwad, Abdul Basit and Akhtar Hussain.

METABOLIC SYNDROME AND RELATED DISORDERS, Volume 7, Number 2, 2009.

2. **Paper 2**

Dietary Patterns Associated with Risk for Metabolic Syndrome in Urban Community of Karachi Defined by Cluster Analysis.

M. Zafar Iqbal Hydrie, Abdul Basit, A. Samad Shera, Rubina Hakeem and Akhtar Hussain.

Pakistan Journal of Nutrition 9 (1): 93-99, 2010. ISSN 1680-5194.

3. **Paper 3**

Detecting Insulin Resistance in Pakistani Subjects by Fasting Blood Samples.

M. Zafar Iqbal Hydrie, Abdul Basit, Asher Fawwad, Muhammad Yakoob Ahmedani, A Samad Shera and Akhtar Hussain.

Accepted in The Open Diabetes Journal.

4. **Paper 4**

Effect of intervention in subjects with high risk of Diabetes Mellitus in Pakistan.

M. Zafar Iqbal Hydrie, Abdul Basit, A Samad Shera and Akhtar Hussain.

To be submitted.

1 Chapter 1. Introduction

1.1 Pakistan – Country Profile

The Islamic Republic of Pakistan was founded in 1947. East Pakistan (now Bangladesh) seceded in 1971. Since independence there have been several military coups. The last was in 1999, when the chief of army staff, Pervez Musharraf, became the chief executive of Pakistan. Mr Musharraf resigned as army chief in November 2007 and stood down as president in August 2008. The general election that took place in February 2008 resulted in a new coalition government led by the Pakistan People's Party and the Pakistan Muslim League (Nawaz); the latter party withdrew from the government in August 2008 (1). Pakistan is a poor and underdeveloped country. A brief overview of the country is given below:

1.1.1 Geography:

The country is located in South Asia, bordering the Arabian Sea, between India on the east and Iran and Afghanistan on the west and China in the north. Geographic coordinates are 30 00 North and 70 00 East. Land area is 769,095 sq km. Population is 150 million according to 2007 official estimates. Pakistan is divided into four provinces, namely Sindh, Baluchistan, Punjab and North-West Frontier Province (NWFP) recently renamed Pakhtoonkowah. Pakistan features different types of landscape; ranging from desert in the south to high mountains in the north. Climate is subtropical and cold in the highlands.

Figur 1 : Geographic Location of Pakistan

1.1.2 Population Demography:

The population of Pakistan was 150 million in 2007 according to government statistics (2). One third of the population lives in urban areas. Sex ratio is 1.05 male(s)/female for the total population.

Population growth rate: 1.88%

Birth rate: 25.6 births/1,000 population

Death rate: 6.8 deaths/1,000 population

Life expectancy at birth for males is 64 years and for females is 68 years.

1.1.3 People:

The five main ethnic groups are Punjabi, Sindhi, Pashtun (Pathan), Baloch and Muhajir (immigrants from India at the time of partition and their descendants). More than 95% of the population is Muslim. Main towns as per June 2003 estimates are Karachi: 10.1 millions, Lahore: 5.6 millions and Faisalabad: 2.3 millions (1).

Languages: Urdu is the national language. English is widespread in business circles and as a second language. Time is 5 hours ahead of GMT.

1.1.4 Education

Education in Pakistan is mostly subsidized by the Government from primary schools to higher education levels in public universities. The definition of literacy is taken as over 15 years of age and able to read and write. This level of literacy for the total population is 48.7% while it is 61.7% for males and 35.2% for females according to 2004 estimates (2).

1.1.5 Economy

Pakistan's economy depends mostly on agriculture. The GDP - per capita (PPP) of the country was $2,600 according to 2006 estimates, but political instability, civil unrest and the threat of terrorist violence have damaged the business operating environment since 2008. The catastrophic flooding of August-September 2010 has only heightened this dependency.

Currency:

Pakistan rupee (PRs); PRs1 = 100 paisa. Average exchange rate in 2009: PRs 81.7:US$1

1.1.6 Lifestyle and Physical Activity

Lifestyle of the people is different depending to rural and urban settings. Apart from household work the women in the rural areas also help their men in the fields and in looking after cattle. Compared to this the people in cities are exposed to a easier way of daily life. Pakistani people do not have a tradition of doing recreational physical exercise apart from the requirements of their daily work.

1.1.7 Karachi

Karachi is the largest and most populous city in Pakistan. The population and demographic distribution in the megacity has undergone numerous changes over the past 150 years. At the time of independence on 14 August 1947, it became the capital city of Pakistan, with a population about 450,000. However, the population rapidly grew with large influx of refugees from neighbouring India (after the partition of British India). By 1951, the city population had crossed one million mark and in the following decade, the rate of growth of Karachi was over 80 percent. Today, the city has grown 60 times its size from 1947 when it became the country's first capital (3).

Predominantly Urdu speaking, the refugees known as Muhajirs form the dominant ethnic group in Karachi. It is the financial and commercial capital of Pakistan; accounting for a lion's share of Pakistan's revenue generation (20% of the GDP of Pakistan).

1.2 Global Burden of Chronic Non Communicable Diseases

While infectious diseases are still threatening people's health, non-communicable diseases (NCDs) – such as cardiovascular diseases, cancers, chronic respiratory diseases and diabetes were responsible for 60% of all deaths globally in 2005 (estimated at 35 million deaths). Total deaths from NCDs are projected to further increase by 17% over the next 10 years (4). Low- and middle-income countries are most likely to be affected by these diseases, which can be prevented by modifying common risk factors such as tobacco use, unhealthy diet, physical inactivity and harmful use of alcohol.

Globally, cardiovascular diseases (CVD) are the number one cause of death with an estimated 17 million people dying from cardiovascular disease in 2005, representing 30% of all global deaths. About 80% of these deaths occurred in low- and middle income countries. The high burden of CVD in developing countries is attributable both to the increased incidence of these disorders as well as the relatively early age at which they occur (5-10). The contribution of developing countries to the global burden of CVD in terms of disability adjusted years of life lost was three times higher than that of developed countries (11).

The global prevalence of people with diabetes is 6.4%, affecting 285 million adults in 2010 and this will increase to 7.7% with 439 million adults affected by 2030 (12). Thus between 2010 and 2030, there will be a 69% increase in numbers of adults with diabetes in developing countries and a 20% increase in developed countries (12). The greatest increase of 195% is projected to be in India (12,13). The last two decades has seen an explosive increase in the number of people diagnosed with diabetes worldwide and 75% of these are from the developing countries (13). Unfortunately this trend of increasing prevalence of diabetes and obesity is imposing a huge burden on our already fragile health-care systems

and this is likely to increase further in the future (14,15). Every year, 3.2 million people around the world die from complications associated with diabetes. Type 2 diabetes has become one of the major causes of premature illness and death, mainly through increased risk of CVD which is responsible for 80 per cent of these deaths (12,16). World Health Organization (WHO) projects that diabetes deaths will double between 2005 and 2030 (4).

1.2.1 Prevalence and Global trends of Diabetes

Diabetes mellitus is the fourth or fifth leading cause of death in most high-income countries and there is evidence suggesting that it is increasing in epidemic proportions in many newly industrialized developing countries (4,12). Complications from diabetes are resulting in increasing disability, reduced life expectancy and enormous health costs for every country making diabetes one of the most challenging public health problems in the 21st century. The low- and middle income countries (LMCs) face the greatest threat from the burden of diabetes with 70% of new incident cases developing in these countries in the future (17,18). Unfortunately, many countries are unaware of the magnitude and future burden due to the increase in diabetes and its complications on their own countries. Table 1 shows the global and projected burden of diabetes and IGT,within the next 20 years.

Tabell 1: **Global Burden: Prevalence and Projections of Diabetes and IGT, 2010 and 2030**

	2010	2030
Total world population (billions)	7.0	8.4
Adult population (20-79 years, billions)	4.3	5.6
Diabetes (20-79 years)		
Global prevalence (%)	6.6	7.8
Number of people with diabetes (millions)	285	438
IGT (20-79 years)		
Global prevalence (%)	7.9	8.4
Number of people with IGT (millions)	344	472

In addition to diabetes, Impaired glucose tolerance (IGT), a condition also referred to as prediabetes is a substantial risk factor for the progression to diabetes and constitutes a major global public health concern, both because of its strong association with diabetes incidence and with its association of increased risk of cardiovascular disease. Moreover, microvascular complications, such as retinopathy, chronic kidney disease, and neuropathy, and cardiovascular disease have been associated with prediabetes (19-22).

Looking at the global trend amongst the ten leading countries with diabetes we see that five of these are from Asia as shown in table 2 which is an alarming senerio for experts working in the region (12,23). Recently the IDF website has shown that China appears to have overtaken India and become the global epicentre of the diabetes epidemic with 92.4 million adults with the disease.

In 2030, China will rank first with an estimated half a billion people with diabetes, followed by India in second place with 87 million people having diabetes (12,24).

Tabell 2. Top 10 countries for numbers of people aged 20–79 years with diabetes in 2010 & 2030.

	2010		2030	
	Country	No. of adults with diabetes (millions)	Country	No. of adults with diabetes (millions)
1	India	50.8	China	500
2	China	43.2	India	87.0
3	USA	26.8	USA	36.0
4	Russian Federation	9.6	Pakistan	13.8
5	Brazil	7.6	Brazil	12.7
6	Germany	7.5	Indonesia	12.0
7	Pakistan	7.1	Mexico	11.9
8	Japan	7.1	Bangladesh	10.4
9	Indonesia	7.0	Russian Federation	10.3
10	Mexico	6.8	Egypt	8.6

1.2.2 Diabetes in Pakistan

The International Diabetes Federation estimates that there are approximately 7 million people with diabetes in Pakistan making it seventh among countries with the highest number of adults with diabetes as shown in table 2 (12). This number is predicted to increase between to 13.8 million by the year 2030 making it fourth amongst this list (12,25). These predictions are modeled upon the reported prevalence of type 2 diabetes (T2DM) in the national survey conducted by the Diabetic Association of Pakistan (DAP) in collaboration with World Health Organization (WHO) during the 1990s (26-29). The national survey was conducted in urban and rural areas in all the four provinces (NWFP, Baluchistan, Punjab and Sindh) of Pakistan using WHO guidelines for the diagnosis of T2DM and IGT in ~ 5,600 persons above 25 years of age. The overall prevalence of T2DM among men and women was reported to be 11%, with overall abnormal glucose control of around 22%.

A summary of the results is given below in table 3.

Tabell 3. Pakistan National Diabetes Survey

Province		Diabetes(%)	IGT(%)
Sindh	(Rural)	13.9	11.2
	(Urban)	16.5	10.4
Baluchistan	(Rural)	07.5	07.4
	(Urban)	10.8	10.4
NWFP	(Rural)	12.0	09.4
Punjab	(Rural)	06.2	05.6
	(Urban)	13.7	10.3
Overall		11.5	9.3

A higher prevalence of obesity and IGT was observed among women vs. men and a relatively higher prevalence of diabetes and IGT was found in younger age groups compared

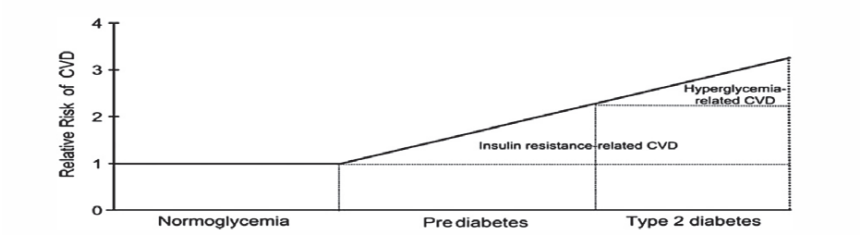
to western populations (26-29). Nearly half of the subjects did not know they had diabetes before the surveys, a finding also seen in other population based studies worldwide (12).

1.3 Metabolic Syndrome (High Risk for Diabetes and CVD Epidemic)

Over the last 3 decades, the prevalence of metabolic syndrome has been increasing steadily in all populations globally (30,31). Despite the debate on use of the term 'Metabolic Syndrome', its significance in helping identify subjects at high risk of developing type 2 diabetes and cardiovascular disease (CVD) is still recognized.

Subjects having metabolic syndrome have a 2–3 fold risk of cardiovascular disease and a five fold risk of developing type 2 diabetes (32). It is estimated that nearly 20-25 per cent of the world's adult population has the metabolic syndrome and they are twice as likely to die from a heart attack and three times likely to suffer from a heart attack or stroke compared with people without the syndrome (32).

This 'clustering' of metabolic abnormalities that occur in an individual appear to confer a substantial additional cardiovascular risk over and above the sum of the risk associated with each abnormality (32,33). Thus more components of the metabolic syndrome that are evident, the higher is the CVD risk as shown in Figure 2 (34,35).



Figur 2. Relative risk of CVD in normoglycemia, prediabetes and type 2 diabetes. (36)

1.3.1 Defination of Metabolic Syndrome

After Reaven put forward the concept of Syndrome X, many attempts have been made to define this clustering of risk factors for cardiovascular disease and type 2 diabetes mellitus with names such as "deadly quartet" and "insulin resistance syndrome" but it has finally been referred to as the "Metabolic Syndrome" (36-41).

In 1998, a WHO diabetes group first attempted to define this syndrome with insulin resistance and impaired glucose tolerance or diabetes as essential components, together with at least two other components (38).

In 1999, the European Group for Study of Insulin Resistance (EGIR) called it insulin resistance syndrome and defined insulin resistance as plasma insulin levels in the upper quartile of the population as a primary requirement (39). Predetermined cut points for the other criteria were used as shown in Table 4 below.

In 2001, the National Cholesterol Education Program, Adult Treatment Panel III (NCEP, ATP III) came up with a more clinical based definition for the metabolic syndrome (40). While insulin resistance was considered important, it was excluded from the definition. The ATP III criteria did not make any single factor necessary for diagnosis, but instead made presence of three of five factors as the basis for establishing the diagnosis; these factors being abdominal obesity, elevated triglycerides, reduced HDL-C, elevated blood pressure and elevated fasting glucose (IFG\type 2 diabetes mellitus).

In 2003, the American Association of Clinical Endocrinologists focused again on insulin resistance as the primary cause behind the primary metabolic risk factors (41). Calling it the insulin resistance syndrome as done by EGIR, the definition included IGT, elevated triglycerides, reduced HDL-C, elevated blood pressure, and obesity as major criteria; while factors such as family history of CVD or type 2 diabetes mellitus, polycystic ovary syndrome and hyperuricemia were needed to make a clinical diagnosis. The decision of defining the syndrome was left on the clinician's judgment.

In 2005, the International Diabetes Foundation (IDF) published its own definition, trying to make the diagnosis clinically simple and widely usable as possible (32). The IDF definition made the presence of abdominal obesity compulsory for diagnosis. Once this essential condition was present, at least two additional factors out of four were necessary for the diagnosis. The IDF definition recognized for the first time ethnic differences in the correlation between abdominal obesity and other metabolic syndrome risk factors (Table 4).

Tabell 4. Previous criteria proposed for the diagnosis of metabolic syndrome

Clinical measure	WHO (1998)	EGIR	ATP III (2001)	AACE (2003)	IDF (2005)
Insulin resistance	IGT, IFG, T2DM, or lowered insulin sensitivity plus any 2 of the following	Plasma insulin >75th percentile plus any 2 of the following	None, but any 3 of the following 5 features	IGT or IFG plus any of the following based on clinical judgment	None
Body weight	Men: waist-to-hip ratio >0.90; women: waist-to-hip ratio >0.85 and/or BMI >30 kg/m^2	WC ≥94 cm in men or ≥80 cm in women	WC ≥102 cm in men or ≥88 cm in women	BMI ≥25 kg/m^2	Increased WC (population specific) plus any 2 of the following
Lipid	TG ≥150 mg/dl (1.7 mmol/l) and/or	TG ≥150 mg/dl (1.7 mmol/l) and/or	TG ≥150 mg/dl (1.7 mmol/l)	TG ≥150 mg/dl (1.7 mmol/l)and	TG ≥150 mg/dl (1.7 mmol/l) or on TG Rx
	HDL-C <35 mg/dl (0.90 mmol/l) in men or <39 mg/dl (1.01 mmol/l) in women	HDL-C <39 mg/dl (1.01 mmol/l) in men or women	HDL-C <40 mg/dl (1.03 mmol/l) in men or <50 mg/dl (1.29 mmol/l) in women	HDL-C <40 mg/dl (1.03 mmol/l) in men or <50 mg/dl (1.29 mmol/l) in women	HDL-C <40 mg/dl (1.03 mmol/l) in men or <50 mg/dl (1.29 mmol/l) in women or

					on HDL-C Rx
Blood pressure	≥140/90 mmHg	≥140/90 mmHg or on hypertension Rx	≥130/85 mmHg	≥130/85 mmHg	≥130 mmHg systolic or ≥85 mmHg diastolic or on hypertension Rx
Glucose	IGT, IFG, or T2DM	IGT or IFG (but not diabetes)	>110 mg/dl (6.1 mmol/l) (includes diabetes)[a]	IGT or IFG (but not diabetes)	≥100 mg/dl (5.6 mmol/l) (includes diabetes)
Other	Microalbuminuria			Other features of insulin resistance[b]	

[a] The 2001 definition identified fasting plasma glucose of ≥110 mg/dl (6.1 mmol/l) as elevated. This was modified in 2004 to be ≥100 mg/dl (5.6 mmol/l), in accordance with the American Diabetes Association's updated definition of IFG.

[b] Includes family history of type 2 diabetes mellitus, polycystic ovary syndrome, sedentary lifestyle, advancing age, and ethnic groups susceptible to type 2 diabetes mellitus.

The AHA/NHLBI statement was released later in 2005 and was popularly known as the modified ATP III definition, with no mandatory criteria which had to be present (42,43). One major change was the reduction from 110 to 100 mg/dl for the diagnosis of IFG; corresponding to the modified American Diabetes Association (ADA) criteria for IFG. The criteria of abdominal obesity was specified by ethnicity and based on the clinician's judgment (Table 5).

Tabell 5. IDF and AHA/NHLBI

Comparison of diagnostic criteria for MS from the International Diabetes Federation (IDF) and American Heart Association (AHA)/National Heart, Lung, and Blood Institute (NHLBI)

IDF clinical criteria for metabolic syndrome		AHA/NHLBI diagnostic criteria for metabolic syndrome	
Measure (central obesity plus any two of five other criteria constitute a diagnosis of metabolic syndrome)	Categorical cut points	Measure (any three of the five criteria below constitute a diagnosis of metabolic syndrome)	Categorical cut points
Central obesity	Waist circumference ethnicity specific For South Asians: ≥ 90 cm in men, ≥ 80 cm in women	Elevated waist circumference	General U.S. population: ≥102 cm (≥40 in.) in men, ≥88 cm (≥35 in.) in women; lower cut points for insulin-resistant individuals or ethnic groups (based on clinical judgment)
Raised triglycerides	>150 mg/dl (1.7 mmol/l) or on specific treatment for this lipid disorder	Elevated triglycerides	≥150 mg/dl (1.7 mmol/l) or on drug treatment for elevated triglycerides
Reduced HDL cholesterol	<40 mg/dl (1.03 mmol/l) in men, <50 mg/dl (1.29 mmol/l) in women or on specific treatment for this lipid abnormality	Reduced HDL cholesterol	<40 mg/dl (1.03 mmol/l) in men, <50 mg/dl (1.29 mmol/l) in women
Raised blood pressure	≥130 mmHg systolic blood pressure or	Elevated blood pressure	≥130 mmHg systolic blood pressure or ≥85 mmHg

	≥85 mmHg diastolic blood pressure or on treatment for previously diagnosed hypertension		diastolic blood pressure or on drug treatment for hypertension
Raised fasting glucose	Fasting plasma glucose ≥100 mg/dl (5.6 mmol/l) or previously diagnosed type 2 diabetes		Fasting plasma glucose ≥100 mg/dl (5.6 mmol/l) or previously diagnosed type 2 diabetes

In the IDF and modified ATP III defination it was evident that ethnicity had a role in influencing metabolic syndrome. Thus different ethnic backgrounds, diet and physical activity, population age and sex structure and levels of nutrition, all have shown to influence the prevalence of the metabolic syndrome (32,43). Although the precise increase in the risk of developing NCDs may vary depending on the population being studied, from a clinical viewpoint the presence of the metabolic syndrome places a person at higher risk for major CVD events and/or T2DM (44). Taking this in a global prespective, it then becomes not only a medical, but also a socio-economic need to take all steps necessary to try and prevent the ravages which can be caused by T2DM and CVD (11,14,44).

1.3.2 Prevalence of the Metabolic Syndrome

The widespread use of the different metabolic syndrome definitions has resulted in a large number of studies describing different prevalence rates of the metabolic syndrome.

The prevalence of the ATP-III metabolic syndrome in the U.S. was initially reported in the Third National Health and Nutrition Examination Survey (NHANES III, 1988–1994). The age-adjusted prevalence was 23.7% (45–49). The contribution of the various components was different among ethnic groups. Low HDL cholesterol, hyperglycemia and high triglycerides made a significantly greater contribution in Mexican-Americans while arterial hypertension was more prevalent in African-Americans. The prevalence of the ATP-III metabolic syndrome was updated in the NHANES 1999–2000. The age-adjusted prevalence increased from 24.1% to 27% (48). An increased prevalence was observed in younger women (< 40 years).

The WHO criteria was used mostly in European cohorts (46,49). The prevalence of the WHO metabolic syndrome in non-diabetic subjects varied between 7 and 36% for men 40–55 years and between 5 and 22% for women of the same age group (49).

Associations between the metabolic syndrome, CHD, and diabetes have also been established by an analysis of the cross-sectional NHANES III data on adults aged >50 years (50). A stepwise increase in the prevalence of the metabolic syndrome was observed with worsening glucose tolerance, and 86% of people with diabetes had the metabolic syndrome (51). The prevalence of CHD was 19% in people with both the metabolic syndrome and diabetes versus 9% in those with neither and 7.5% in the small percentage of the study

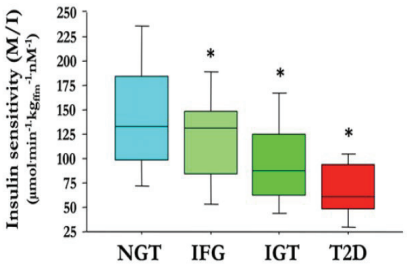
population that had diabetes but not the metabolic syndrome. These results suggest that for most diabetic patients, cardiovascular risk is related not to diabetes itself but to the concomitant presence of the metabolic syndrome (52).

The currently available definitions can be used as valuable tools for studying the disease pattern, even these definitions include, in affected and non-affected subjects a heterogeneous group of cases with a broad range of relative risks for future complications, which need to be explored.

Finally, the metabolic syndrome could be considered as a prime target for preventive medicine. Clearly, the emerging global epidemic of metabolic and vascular disease has significant implications for the development of population based health promotion strategies. Lifestyle modifications and weight loss programs are a key part of the program because weight loss reduces the incidence of type 2 diabetes and a large percent of the affected subjects had excess body weight (53). Thus preventive programs, properly designed need to be implemented, otherwise we will continue to treat the majority of the cases when they reach the steeper extreme of the road: where many present with the complications of the metabolic syndrome such as diabetes complications and heart diseases.

1.3.3 Metabolic Syndrome in South Asians

In Asia the prevalence of the metabolic syndrome is in the range of 10% to 40% (54–58). Insulin resistance and clustering of other proatherogenic factors (the metabolic syndrome), is frequently seen in South Asians and these important contributory factors for T2DM and CHD make South Asians more prone to develop these diseases (58-60). Insulin resistance, at the level of the liver and peripheral tissues, and defective glucose sensing at the b-cell are the central pathophysiologic determinants that together cause and predict the defining hyperglycemia as is evident in figure 3. All of these factors are fueled by increasing obesity resulting from nutritional and lifestyle transitions (61).



Figur 3. Insulin sensitivity (as box plots of the M/I)

in individuals with NGT, impaired fasting glucose (IFG), IGT, and type 2 diabetes (T2D). Asterisks indicate a significant difference from the NGT group (61).

Prevalence of obesity is rising in South Asia and this important factor is associated with insulin resistance since a increase of over one third ideal body weight decreases insulin sensitivity by 40% (62). There are other factors related to insulin resistance that also increase susceptibility to CHD in South Asians such as high levels of proatherogenic small, dense low-density lipoprotein (LDL) as observed in Asian Indians (63,64).

Studies from India shows that about one third of the urban population has the metabolic syndrome and consequently the prevalence of T2DM has become double during the previous 3 decades (57, 65-68). Around 15% of the global mortality from CVD is also contributed by India and preventing metabolic syndrome could make a significant difference in reducing this also (69). The Southall study done in UK demonstrated that despite being matched for age and body mass index (BMI) with Caucasians, South Asian men had higher waist: hip ratio, higher systolic blood pressure (BP), higher insulin levels after glucose load, higher triglyceride levels and lower high density lipoprotein (HDL)-levels, all suggesting a high prevalence of the Metabolic Syndrome (53). In addition, type 2 diabetes a CHD risk equivalent was present in 20% of the South Asians compared to 5% of Caucasians adding to the CVD risk burden (70). This only highlights the increased risk that south asians have at lower thresholds and by making a diagnosis of the metabolic syndrome we might be able to initiate lifestyle changes earlier, to reduce the risk of CVD and T2DM in this population.

1.3.4 Metabolic Syndrome in Pakistan

Very few studies have looked at the prevalence of metabolic syndrome in Pakistan. One study done in rural area of Pakistan showed that in total 40% of the subjects met the IDF definition while 31% met the ATP III definition of the metabolic syndrome (71). Another recent population based study carried out in an urban area, Karachi of Pakistan showed metabolic syndrome at a prevalence of 34.8% according to the International Diabetes Federation (IDF) definition and 49% by the modified National Cholesterol Education Program, Adult Treatment Panel III (NCEP ATP III) criteria (72).

In another study done in 400 subjects at a tertiary cardiology unit in Pakistan, the prevalence of the metabolic syndrome according to ATP III was 44% (73). While in another study also done in Karachi, 46% type 2 diabetic subjects were found to have metabolic syndrome according to the WHO definition (74).

1.4 Associated Factors for Diabetes and Metabolic Syndrome

Rapid demographic and nutritional changes with increased life expectancy and more elderly population is occuring globally. Most importantly, globalization of diets and consumption of nontraditional fast foods is taking place at a very rapid pace especially in urban areas

(14,75). A progression of these transitions and changes in populations of many countries is resulting in high prevalence of non-communicable diseases such as diabetes. Looking at developing countries we see that rapid increase in western fast food outlets and increased consumption of fried snacks is taking place (61,75). Furthermore, migration from villages to cities is increasing in these countries resulting in nutritional imbalance, physical inactivity, stress, and increased consumption of alcohol and tobacco (76-79). In addition, some populations such as south asians are physically less active leading a increasingly sedentary lifestyle which has further deterimental effects on their health (80-81).

Thus some of the modifiable and non-modifiable risk factors contributing to type 2 diabetes as evident from various studies are shown in table 6 below.

Tabell 6 Modifiable and non-modifiable risk factors and associated disorders for Type 2 diabetes

Modifiable risk factors	Non-modifiable risk factors
Overweight* and obesity† (central and total)	Ethnicity
Sedentary lifestyle	Family history of Type 2 diabetes
Previously identified glucose intolerance (IGT and/or IFG)	Age
Metabolic syndrome:	Gender
Hypertension	History of gestational diabetes
Decreased HDL cholesterol	Polycystic ovary syndrome
Increased trigylcerides	
Dietary factors	
Intrauterine environment	
Inflammation	

*World Health Organization (WHO) criteria define overweight as a BMI ≥ 25 kg/m^2 [50].
†WHO criteria define obesity as a BMI ≥ 30 kg/m^2 [50]. For country/ethnic specific values for waist circumference as a measure of central obesity see table 4.
HDL, high-density lipoprotein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

It is important to remember that modifiable risk factors such as overweight and obesity, sedentary lifestyle, unhealthy diet, glucose intolerance, alcohol consumption, and tobacco smoking can be targeted for prevention of disease, and by controlling these risk factors through population based prevention programs we can reduce the disease burden (82).

1.4.1 Socio-demographic Factors

These include factors such as age, sex, family history of type 2 diabetes, genetic predisposition, history of gestational diabetes, and ethnicity etc. All of these belong to the nonmodifiable risk factors for type 2 diabetes but are mentioned here because they are important. The risk of type 2 diabetes increases markedly with age and unfortunately the age of onset of type 2 diabetes has steadily decreased down into younger adults and even adolescents in recent decades (82).

Also the magnitude of the differences between Caucasians and South Asians when exposed to same environments implies a significant genetic contribution in them (70). Thus there is strong evidence that South Asians have a stronger genetic predisposition to diabetes than other ethnic groups. People who have family members with type 2 diabetes are at greater

risk for developing diabetes themselves as is evident from a study done in Pakistan which showed that 45% people with diabetes had a positive family history of diabetes (83).

1.4.2 Overweight and Obesity

Obesity has been identified as the single most important risk factor for Type 2 diabetes. The WHO estimates that there are currently 1.1 billion people who are overweight with estimations of over 1.5 billion by 2015 (84). Longitudinal studies have shown obesity to be a powerful predictor for type 2 diabetes (84-85). This is further strenghten by the fact that interventions aimed at reducing obesity also reduce the incidence of Type 2 diabetes.
The average BMI value in South Asians is lower than seen in white Caucasians, Mexican-Americans, and blacks, but unfortunately South Asians have a higher percentage of body fat compared to white Caucasians and blacks at this lower BMI values (57,59,70).
Because of this increased cardiovascular risk among Asian people occuring at lower waist circumference compared to European populations, both the WHO and the IDF have adopted the definition of overweight and obesity in Asians at a BMI of 23 kg/m2 or above and 25 kg/m2 or above, respectively, while central obesity is defined as a waist circumference of 90 cm or above in men and 80 cm or above in women (59).

1.4.3 Nutritional transition

Work patterns changing from heavy labour to sedentary due to increase in computerization and mechanization, and improved transport have made an impact on human health (14). These sedentary changes along with easy access to fast foods and empty calories have resulted in increased rates of obesity and type 2 diabetes globally (44,84-86). Although it is difficult to collect accurate dietary data, epidemiological studies indicate that a high calorie and low dietary fibre intake with a high glycaemic load and low polyunsaturated to saturated fat ratio contribute towards developing chronic diseases such as type 2 diabetes and metabolic syndrome (61,867-88). Thus diet is a crucial aspect of lifestyle changes.
South Asians consume more carbohydrates compared to Europeans and this may lead to hyperinsulinemia, postprandial hyperglycemia, hypertriglyceridemia and low HDL cholesterol levels, all of which is probably due to insulin resistance (87). Particularly in South Asians the increased carbohydrate and fat intake, along with decreased fiber intake likely contributes to obesity, the metabolic syndrome and T2DM (61,87,89). Studies have shown that high intake of whole grain foods or cereal fibers reduce the risk of diabetes and even adjustments in diet composition without weight loss could improve hyperglycemia of diabetes (90,91).

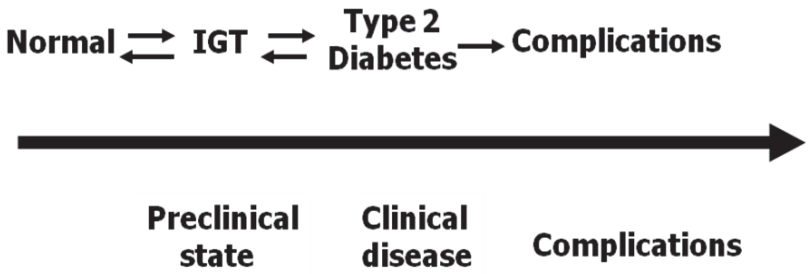
1.4.4 Physical Activity and Sedentary Lifestyle

Physical activity has decreased over recent decades in many populations, and this is a major contributor to the current global rise of obesity. Physical inactivity has been found to be an independent predictor of Type 2 diabetes in both cross-sectional and longitudinal studies (81,82).

Unfortunately South Asians have been found to be more sedentary compared to other ethnic groups (80,92-97). Increasing sedentary lifestyle is attributed to increased mechanization at workplaces and in household work. Leisure-time activities have also shifted from outdoor play to indoor entertainment such as television and computer games (94). Previously adolescents playing outdoor games regularly and doing household activities had lower prevalence of been overweight, compared to 3 times higher in those not participating in outdoor games (98). Even for equivalent degrees of obesity, more physically active subjects have a lower incidence of diabetes.

1.4.5 Glucose Intolerance (IGT and\or IFG)

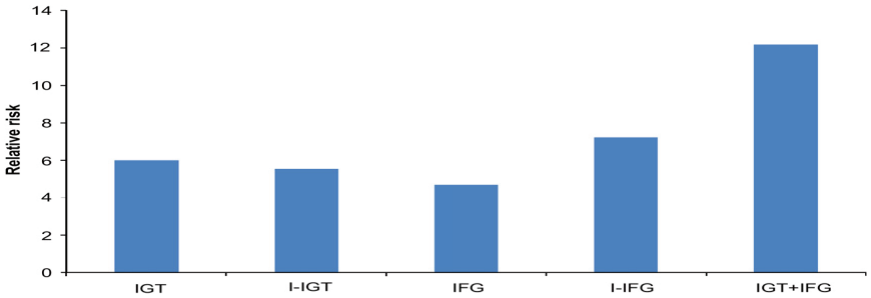
Prediabetes includes the diagnostic categories of IFG and IGT, but is actually a band of glucose concentrations over a continuum extending from conventional NGT to overt type 2 diabetes as shown below.



Prediabetes (IFG and/or IGT) should be viewed as a preclinical state in the natural history of disordered glucose metabolism rather than as a distinctive clinical entity representing an interim condition and as a risk factor prestaging (a) the development of diabetes (increased risk for diabetes) and (b) an increase in cardiovascular and possibly microvascular complications.

The transition from prediabetes to diabetes may take many years but can also be rapid (99,100). Current estimates indicate that up to 70% subjects with prediabetes eventually develop diabetes (101). The International Diabetes Federation estimates that some 344 million people have IGT worldwide in 2010, the vast majority of who live in low- and middle-income countries. By 2030, the number of people with IGT is projected to increase to 472 million as shown in Table 1 (12).

Studies have observed that the risk of developing diabetes as well as the incidence of diabetes is highest in individuals with combined IFG and IGT (Relative risk is 12-fold higher) as shown in figure 4 below (100-102). The average risk of developing diabetes is about 5% to 10% per year in individuals with IFG or IGT compared with approximately 0.7% per year in normoglycemic individuals (102).



Figur 4. Relative risk of developing diabetes in different categories of prediabetes.

Reference group is those with normal glucose tolerance (defined in each study). I-IGT, isolated IGT; I-IFG, isolated IFG; IGT 1 IFG, combined IFG and IGT. (102)

Diagnosing prediabetes helps to identify a segment of the population which is at increased risk for developing both diabetes and CVD so that interventions can be initiated. Diagnosis has traditionally been made by measuring blood glucose levels during either fasting or an OGTT. Many high-risk subjects (pre-diabetes) have a clustering of other cardiovascular disease risk factors, e.g. abdominal obesity, elevated levels of total triglycerides, low levels of high-density lipoprotein (HDL) cholesterol and elevated blood pressure, commonly known as the metabolic syndrome (31,32,42).

1.5 Follow-up studies of Metabolic Syndrome (Prediction of DM and CHD)

Results from large, prospective studies suggest that the metabolic syndrome is an important risk factor for CHD and type 2 DM, and it increases cardiovascular and total mortality (103). A 12-year follow-up data of 2682 middle-aged finnish men showed that death from cardiovascular disease was 2.9–4.2 times more likely among men with metabolic syndrome than those without metabolic syndrome at start of study (104).

Since detecting subjects at risk of future disease and implementing programs to reduce the risk of progression to disease is a fundamental objective of preventive medicine, the metabolic syndrome can be used as a predictor to identify subjects at high risk of developing CVD and diabetes. The dysglycemia of type 2 diabetes coexists with other metabolic abnormalities such as obesity, dyslipidemia, and hypertension, leading one to postulate that

the increased CVD risk in subjects with prediabetes may be largely due to the coexistence of other metabolic syndrome components (43).

Several studies have shown that the metabolic syndrome predicted T2DM independent of other factors (105–109). Lorenzo et al. showed that the odds ratio (OR) using different definitions of the metabolic syndrome (ATP III [OR 2.00], IDF [OR1.69]), and the World Health Organization (WHO) [OR 1.73]) were almost similar in predicting incident CHD independent of age, sex, ethnic origin, history of CHD and T2DM, non-HDL-C, smoking status, and family history of myocardial infarction (110). Subjects free from CHD and/or CHD risk equivalents, when evaluated with ATP III, IDF, and WHO definitions, were also shown to have similar ORs for predicting CHD. Although some studies have shown that conventional risk factors may also predict T2DM or CHD, it appears that the metabolic syndrome adds to the prediction provided by individual components (111–114).

Sattar et al. showed strong association of the metabolic syndrome with diabetes (RR, 7.47) in South Asians, however, with CHD it was less strong (RR, 1.27) (112). Forouhi et al. showed higher cardiovascular risk in South Asians compared to white Caucasians (114). The awareness of ethnicity as a potential independent risk factor for chronic disease has clinical importance because lower thresholds would have to be considered when planning primary prevention strategies in certain populations.

1.6 Intervention Epidemiology

Importance of identifying ssubjects at high risk for developing diabetes has increased with expansion of knowlegde from prevention trials that prevent or delay type 2 diabetes using lifestyle modification or medication (82). The cardiometabolic risk factors, including increased body mass index (BMI), blood pressure, and triglycerides, which often coexist in subjects with IGT and IFG can be modified as shown by prevention studies.

Most interventions targeted preventing Type 2 diabetes by achieving and maintaining a healthy body weight through a combination of dietary measures and physical activity in high risk subjects (pre-diabetes group) (82). Dietary recommendations across studies are quite similar, and stress reducing fat intake and increasing vegetable consumption with moderate calorie restriction in overweight/obese populations. The approach used to promote physical activity in the interventions range from providing exercise goals and advise on how to increase daily physical activity, to providing weekly supervised exercise training sessions. Most interventions recommend a minimum of 30–40 min of moderate physical activity on all or most days of the week.

Tabell 7 Summary of major diabetes intervention studies

Study	Intervention	*n*	Relative risk reduction of T2DM vs. placebo (%)	Duration (years)
Malmö [23]	Lifestyle	181	63	6
Da Qing [24]	Lifestyle	577	42	6
DPS [17,25]	Lifestyle	522	58	3
DPP [18]	Lifestyle	3234	58	3
Japanese study [54]	Lifestyle	458	67	4
Indian study [28]	Lifestyle	531	28	3
DPP [18]	Metformin	3234	31	3
Indian study [28]	Metformin	531	26	3
Indian study [28]	Metformin + lifestyle	531	28	3
TRIPOD [31]	Troglitazone	266	55	2.5
DPP [18]	Troglitazone	3234	75	1
STOP-NIDDM [29]	Acarbose	1429	25	3
XENDOS [34]	Orlistat	3305	37	4
DREAM [32]	Rosiglitazone	5269	60	3

DPP, Diabetes Prevention Program; DPS, Diabetes Prevention Study; STOP-NIDDM, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus; T2DM, Type 2 diabetes mellitus; TRIPOD, Troglitazone in Prevention of Diabetes; XENDOS, XENical in the Prevention of Diabetes in Obese Subjects.

Clinical trials have proven that prevention of type 2 diabetes with lifestyle intervention is possible as shown in table 7, if high-risk subjects who might benefit from preventive interventions are used. Identification of such subjects through invasive blood tests, such as the OGTT, is however not feasible at the population level.

One approach for identifying subjects at high risk for developing diabetes is the use of simple non-invasive scores. Because these scores can predict risk without requiring medical or invasive measures, they can be easily applied to and used by the general public and offer potential for mass screening programs (82). These risk tools can be used to identify people at high risk who can be offered a lifestyle program or become the first step in a 2-step screening procedure in which the risk tool is used to identify people who require further testing (82). Thus further blood glucose testing can be done into a reconfigured score to increase the accuracy of risk prediction.

Several risk tools have been developed across different populations. The first tool for predicting diabetes was Finnish Diabetes Risk Score (FINDRISC), and subsequently other tools have been developed in different countries (82). Variables included in determining risk are generally similar and include age, weight (body mass index, waist circumference), history of hypertension and high blood glucose levels (including gestational and pre-diabetes), and level of physical activity.

The IDF plan for the prevention of Type 2 diabetes is based on controlling modifiable risk factors and can be divided into two target groups:

- people at a high risk of developing Type 2 diabetes;
- the entire population.

The high risk approach consists of 3 steps and is used in most primary prevention trials. However, in planning national measures for the prevention of Type 2 diabetes, both groups should be targeted simultaneously. In addition, it is important that all activities are tailored to the specific local situation based on the cultural specifications.

Preventive measures should be particularly vigorous for those with family history of obesity, T2DM, or premature CHD the so called high risk population. Overweight individuals and those with abdominal obesity should be actively encouraged to lose weight by lifestyle measures.

Research on metabolic syndrome in South Asians should be targeted; initially to observe the prevalence of metabolic syndrome or high risk subjects in the community and to identify the associated risk factors for diabetes and CVD. The metabolic syndrome should be considered as a prime target for preventive medicine. The primary management goals of the metabolic syndrome are to reduce the risks of cardiovascular disease and diabetes burden. This can be followed by prospective intervention studies to ascertain the effect of intervention to prevent T2DM in these high risk subjects.

A high prevalence of the metabolic syndrome in South Asians suggests a higher risk of developing cardiovascular and diabetes in the future. Despite the challenges involved in day-to-day life, the intervention to prevent diabetes is needed in Pakistan due to increased inherent genetic predisposition, younger age of onset of disease, lack of capacity and resources to treat the condition effectively at the primary health-care level.

Targeting subjects with IGT for lifestyle interventions focused around increasing activity and altering dietary factors has been particularly effective and primary prevention trials have produced significant results in people at high risk of diabetes. This has also lead to recommendations been proposed by some for primary prevention in subjects with prediabetes as shown in Table 8 below.

One of the major difficulties in translating knowledge generated by randomized clinical trials (RCTs) is the inability to generalize to the practice setting as they were conducted in a controlled environment. Attempting to translate interventions from studies into a practical setting of diverse nature with less funding which leads to deviations from the initial intervention protocols has resulted in a variety of new approaches which is a challenge for public health experts.

Tabell 8: Key features of selected published recommendations on prediabetes

	ADA Consensus Statement (2007)	Indian Health Services Guidelines for Care of Adults with Prediabetes and/or the Metabolic Syndrome in Clinical Settings (2006)	Australian Diabetes Society and Australian Diabetes Educators Association Position Statement (2007)
IFG	FPG > 100 mg/dL (5.6 mmol/L) but < 126 mg/dL (7.0 mmol/L) and 2-h plasma glucose < 200 mg/dL (11.1 mmol/L)	FPG > 100 mg/dL (5.6 mmol/L) but < 126 mg/dL (7.0 mmol/L)	FPG > 110 mg/dL (6.1 mmol/L) but < 126 mg/dL (7.0 mmol/L) and 2-h plasma glucose < 140 mg/dL (7.8 mmol/L)
IGT	FPG < 126 mg/dL (7.0 mmol/L) and 2-h plasma glucose > 140 mg/dL (7.8 mmol/L) but < 200 mg/dL (11.1 mmol/L)	2-h plasma glucose > 140 mg/dL (7.8 mmol/L) but < 200 mg/dL (11.1 mmol/L)	FPG < 126 mg/dL (7.0 mmol/L) and 2-h plasma glucose > 140 mg/dL (7.8 mmol/L) but < 200 mg/dL (11.1 mmol/L)
Who should be screened for diabetes?	Individuals with risk factors for diabetes should be screened for prediabetes	Annual testing of individuals at risk for developing diabetes	Incidental detection when screening for diabetes
Method of Screening	FPG 2-h OGTT if metformin therapy is considered	FPG Optional 2-h OGTT if resources permit	Incidental detection when screening for diabetes
Recommended Treatment	Lifestyle modification for IFG or IGT Lifestyle modification and/or metformin for IFG and IGT and at least one of the following: age <60years, BMI >35kg/m2, family history of diabetes in first degree relatives, elevated triglycerides, reduced HDL-C, hypertension, HbA1c >6.0%	Lifestyle changes Consideration of metformin on an individualized basis; depression screening and cardiovascular risk reduction also recommended	Intensive lifestyle intervention for a minimum of 6 months before consideration of pharmacotherapy
Follow-up	Metformin treatment: semiannual HbA1c Lifestyle intervention: annual follow-up	Monitor glucose values every 6 months	75-g OGTT, initially performed annually, then indivudualized retesting every 1-3 years

Data from American Diabetes Association. 2010 Standards of medical care in diabetes. Diabetes Care 2010;33(Suppl 1):511-61.

1.7 Rationale or Statement of Problem

Pakistan has been undergoing demographic, epidemiological and nutritional transition for the last few decades. Increased access to energy dense foodstuffs and reduced physical activity has resulted due to so called “urbanization” and “westernization”. Pakistan is also one of the top 10 countries with the most people with diabetes and this current state of affairs will take it in the top 5 countries list by 2030 (12).

Since the metabolic syndrome is postulated to be a precurser of type 2 diabetes and CVD, it seems that in view of the increasing prevalence of type 2 diabetes, there will be high number of subjects with metabolic syndrome in Pakistan. Although the prevelance of metabolic syndrome has been reported to be 44% to 46% in studies done in Pakistan, it has been done in cardiac and diabetic subjects (75,76). No population based epidemiological study had been done in the urban areas of Pakistan to find the prevalence of metabolic syndrome and its associations with the risk factors of T2DM and CVD.

The current epidemiological study will help to assess the prevalence of metabolic syndrome in the general population and look at the associated risk factors, as well as establishing baseline cutoff values for insulin sensitivity. This will help in understanding the volatile high risk situation of future disease burden and lay the foundation for planning intervention studies of primary prevention of Type 2 diabetes and CVD.

Epidemiological evidence have suggested that unless effective prevention and control programmes are started, the prevalence of diabetes will continue to rise globally (82). The collective results of primary prevention trials have showed an average reduction of 51% in new cases of diabetes in high risk subjects (82). Individuals usually at highest risk for diabetes are those having prediabetes i.e. impaired fasting glucose (IFG) and⁄or impaired glucose tolerance (IGT) . Thus identifying high risk subjects and initiating lifestyle intervention are important primary prevention strategies globally.

Since diabetes is increasing at a rapid rate in Pakistan with alarming consequences, prevention is becoming highly relevant over here where subjects have increased inherent genetic predisposition and younger age at onset of disease. We lack the resources to effectively treat the condition at the primary healthcare level and also lack equitable access to healthcare for treating the complications which arises from diabetes. This makes a strong case for investment in diabetes prevention to reduce the future disease burden (44,72,82).

1.8 Research Questions and Objectives of the Study

1.8.1 Research Questions

What is the prevalence of metabolic syndrome based upon WHO, ACE, EGIR, modified ATP III and IDF definition in this Pakistani population?

What is the prevalence of diabetes and other forms of abnormal glucose tolerance in subjects aged 25 years and above in Karachi, Pakistan?

What is the insulin resistance cutoffs for our population?

What is the distribution and relationship of diet with metabolic syndrome in this population?

What is the rate of conversion of IGT to diabetes?

What effect does intervention (lifestyle modification and lifestyle modification with metformin) has on the onset of type 2 diabetes in an urban setting?

1.8.1.1 Main Objective

- To determine the prevalence of metabolic syndrome in a sample of adults aged 25 years and above from an urban population of Karachi.

- To observe the rate of conversion of IGT to diabetes and to observe the impact of intervention (lifestyle modification and combining lifestyle modification with metformin) on the onset of type 2 diabetes in an urban population.

1.8.1.2 Specific Objectives

More specifically, the objectives of the two studies were to:

Estimate and compare the differences in prevalence of metabolic syndrome based upon modified ATP III and IDF definition in Pakistani population.

Estimate the prevalence of diabetes and other forms of abnormal glucose tolerance and association with metabolic syndrome.

Assess the relationships of diet with metabolic syndrome and its risk in this population.

To evaluate the impact of intervention with lifestyle modification.

To note the usefulness of adding an insulin sensitizer (Metformin 500 mg BD) in this population with lifestyle modification and register the benefits of combining them.

1.9 Justification of the Study

It has been noted that the features of Metabolic Syndrome may present up to 10 years preceding Type 2 diabetes and CVD (103-110). Especially in South Asians having a high prevalence of the Metabolic Syndrome may lead to a high diabetes and CVD incidence in the coming decade (57,58).

The increasing prevalence of obesity in recent years along with metabolic syndrome has increased the risk of developing Type 2 diabetes and CVD manifold. Identifying the risk factors associated with Metabolic Syndrome is thus important if primary prevention programs for diabetes and CVD are to be planned in the future.

The identification of risk factors especially modifiable ones would be a integral and vital part of public health polices on prevention as longitudinal studies have shown that reducing these risk factors delays or prevents the occurrence of disease in the future.

The clustering of these risk factors in the so called “metabolic syndrome” may also provide the primary care physician an integrative view of linking conditions together so as to treat these high risk subjects much earlier. This identification of cluster of risk factors may also help in identifying high risk subjects in whom intervention can be done.

Once these high risk subjects are identified, initiating intervention in such primary prevention program could be initiated and culturally adapted needs in such a pioneer program would be observed and documented for future health policy planning.

Unless such culturally adapted effective primary prevention programmes are designed and implemented, the prevalence of diabetes will continue to rise steeply.

The first step should be a primary prevention study of a smaller scale, the results of which are to be analysed and if needed modified according to local needs to initiate local or national health care policies.

2 Chapter 2: Material and Methods

2.1 Study Sites

Two studies were consequently undertaken with different study designs; the first an epidemiological survey in one area of karachi in 2004 followed by the second, a prospective intervention study done between 2006-2009 in karachi.

The first was an epidemiological survey designed to see the prevalence of metabolic syndrome and its risk factors among 500 randomly selected households in Lyari, an urban area within Karachi city in 2004 . The second was a primary prevention study done in the city of Karachi from 2006-2009. It was a prospective randomized clinical trial (RCT) to assess the effect of intervention for 18 months on high risk subjects.

2.2 Research Setting

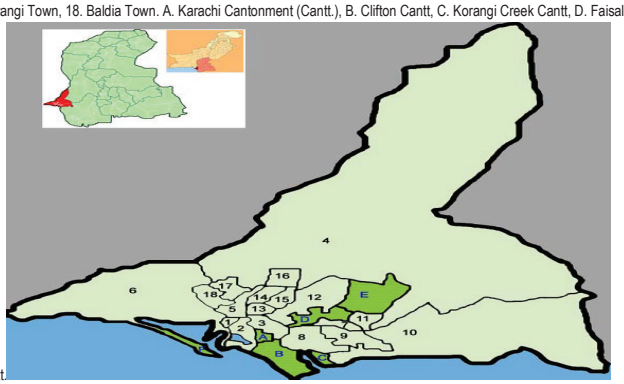
2.2.1 Epidemiological survey in Lyari town:

The City of Karachi is divided into 18 towns as shown in figure 5 and Lyari Town is one of the oldest and most densely populated part of Karachi city. Lyari's approximately 700,000 residents form an extremely diverse community, representing almost every cultural and ethnic groups found in Pakistan. There is a wide spectrum of socioeconomic groups.

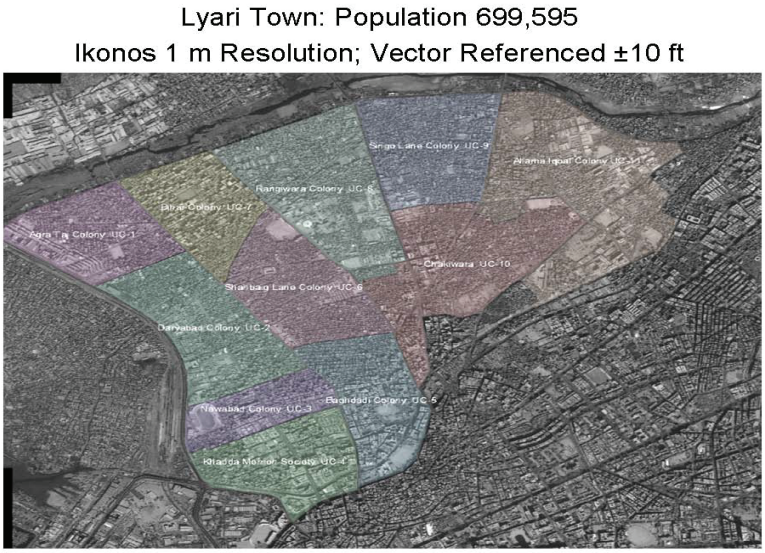
2.2.2 Primary Prevention Study in Karachi city

Karachi is the largest and most populous city in Pakistan. The City of Karachi is divided into 18 towns and 178 union councils. Today the population of this megacity is somewhere around 16 million.

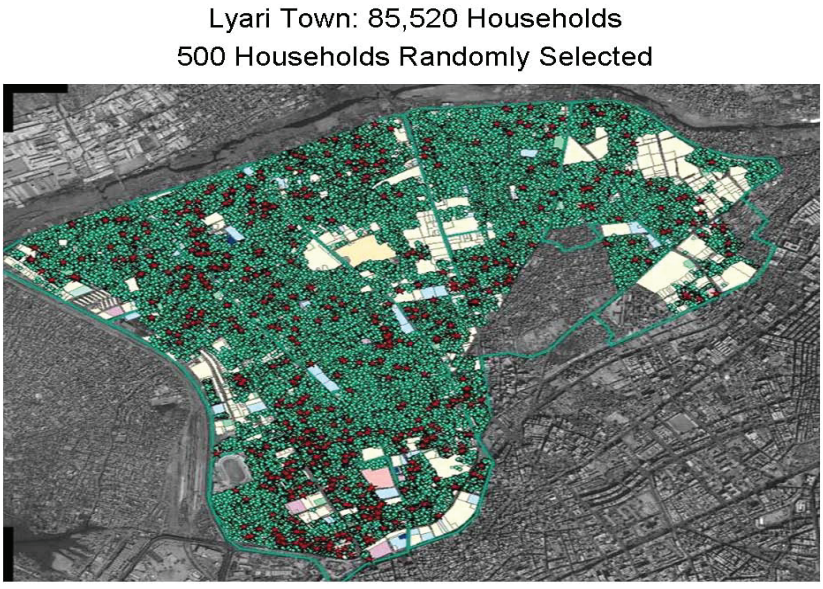
1. Lyari Town, 2. Saddar Town, 3. Jamshed Town, 4. Gadap Town, 5. SITE Town, 6. Kemari Town, 7. Shah Faisal Town, 8. Korangi Town, 9. Landhi Town, 10. Bin Qasim Town, 11. Malir Town, 12. Gulshan Town, 13. Liaquatabad Town, 14. North Nazimabad Town, 15. Gulberg Town, 16. New Karachi Town, 17. Orangi Town, 18. Baldia Town. A. Karachi Cantonment (Cantt.), B. Clifton Cantt, C. Korangi Creek Cantt, D. Faisal Cantt, E. Malir Cantt, F. Manora Cantt.



Figur 5: Description of the 18 towns and 6 cantonments of Karachi.



Figur 6: Lyari Town



Figur 7: Lyari Town 500 Households randomly selected

2.3 Study Population

2.3.1 Lyari Town

We generated a computerized random sample of 500 households from among the 85,520 households in Lyari Town as shown in figure 6. There were 11 union councils in Lyari Town

where the samples were taken from ensuring that each union council had equal opportunity to be represented in the sample selection. We expected approximately 1000 adult men and women 25 years and above in the 500 households selected in Lyari Town as shown in figure 7. If members of a household that had been selected refused to consent to household interviews, we knocked on the third door to the right of that house (while standing facing the door of the original house) and seeked consent there. If we were refused again, we knocked on the next consecutive door to the right and repeated this process until we had enrolled a household from the neighbourhood of the original household selected.

2.3.1.1 Criteria for Inclusion and Exclusion

All adults 25 years and above from the selected households who gave their informed consent were included in the study.

Persons with physical or intellectual disabilities that precluded participation in the study were excluded and also those who had resided in the current address for less than 6 months before the survey.

2.3.2 Karachi City

Karachi is the largest and most populous city of Pakistan. All the major ethnic groups of the country are represented here. High risk questionnaires were distributed at the out patient departments of health care centres to recruit the family members of known diabetes subjects. Posters, banners and leaflets informing about the primary prevention program were distributed throughout the city. Our team of health professionels also visited different organizations and offices to generate awareness about our primary prevention program and gave awareness lectures. Diabetes screening camps were also arranged at various public places such as parks and community halls to create awareness about diabetes and inform the general public about the prevention program.

2.3.2.1 Criteria for Inclusion and Exclusion

Subjects over the age of 30 years who fulfilled the study criteria were included. Subjects having IGT and no known diabetes were included.

Subjects with a debilitating disease or compromised condition such as cancer or hepatitis etc, which could be a contraindication to participate in such a trial were excluded.

Those taking any medication which could affect their blood glucose levels such as beta blockers for hypertension etc, or planning to get pregnant were also excluded from the study.

2.4 Sample Size

2.4.1 Lyari Town

In the planning phase of the study the following assumption was made by the research group of the epidemiological survey;

Assuming that the prevalence of T2DM to be 11% in this population and the size of the population from which the study sample is to be selected (persons 25 years and above in Lyari Town) is 244,000. The worst acceptable result is ±1.5% from the true population value, thus our study would require a sample of at least 713 individuals to have 80% power to detect the true population value.

Individual members within households also reserve the right to refuse participation in the study. Assuming a 10% refusal rate (by members within the household at the time of interview) and another 10% refusal rate by those who decline to provide consent for a blood test, we expected at least 810 individuals to participate in this study.

Since the prevalence of metabolic syndrome is assumed to be higher than that of diabetes we believe this sample size would be sufficient for assessing metabolic syndrome in our population.

In the field we were able to interview 867 individuals; more than the required number needed but only 363 individuals gave blood samples leaving us with less than the required numbers at the end of the study having 40 – 45% power to detect true population value.

2.4.2 Karachi City

For the primary prevention study nearly 2000 suspected high risk cases identified by a high risk questionnaire were to be invited to participate. Considering 30% IGT cases in high risk individuals around 600 were expected to have IGT. The IGT cases were then to be randomly allocated on three different arms, two preventive groups and one control group, all with 200 participants. With an expected conversion rate of nearly 30% T2DM in the control group (n = 60) and an reduction of 15-20 % in the intervention group (n = 9 -12) the sample size will be adequate considering ß = 0.20 and $\alpha = 0.05$.

Although an estimated 5000 people attended the diabetes prevention lectures and visited the screening camps and around 2300 people filled in the high risk questionnaire only 1825 were identified as high risk on the basis of the questionairre. Of these 1739 high risk subjects undertook a standardized oral glucose tolerance test (OGTT) and 317 subjects were identified as having impaired glucose tolerance (IGT group) and were randomized into the three groups.

2.5 Research Design

2.5.1 Lyari Town

2.5.1.1 Survey protocol and procedures

The survey activities were conducted over a period of 6 months from July to December 2004. A Geographical Imaging Systems (GIS), previously developed for Lyari Town with unique identification numbers ascribed to 85,520 households was used.

The survey activities were divided into two phases—the household interview plus physical examination and blood sample collection.

A household was defined as including all those who shared a kitchen. Five hundred households were randomly selected through the GIS software and maps to these households were generated for 9 field teams. A field team comprised of one or two medical students, a female health worker and a male health worker. Surveyors from the GIS teams worked as guides for 2-3 teams in a given area. All teams and surveyors were supervised by a medical doctor acting as the field coordinator.

2.5.1.2 Household census and interview

Twelve medical students conducted these household visits with the assistance of 8 health workers from Lyari Community Development Project – a local welfare organization. Once a household was located, medical students identified themselves to the oldest male or female member present and informed them of the objectives of the survey. All adults 25 years and older were invited to participate after providing signed consent. In case of illiterate participants, the consent form was read out to them and a thumb print procured in the presence of a household member or neighbour as witness.

Field work entailed afternoon visits to the selected household by a field team (medical students and health worker), introduction to the purpose of the research study, consent, interviews and physical measurements (including weight, height, waist and hip circumference, blood pressure).

The interviewers made a minimum of 2 visits and up to 5 visits before a household was classified as a non contact. Where possible, at each participating household a personal interview was conducted with every adult member aged 25 years and above who met the eligibility requirements.

At the end of the household visit, all adults 25 years and above were asked to undertake an 8 hour fast for blood tests (fasting blood sugar and lipid profile) that was collected at home on Saturday and Sunday mornings. All adults were provided with a urine collection bottle and asked to collect a mid-stream urine specimen for tests (pus cells, proteinuria and microalbuminuria) on the morning of their blood test date.

2.5.1.3 Questionnaire

The adults present in each household were administered a survey form (Questionnaire) which consisted of 3 main parts.

Part A collected information about the entire household and was same for all the persons living in a specific household. It consisted of 4 sections.

Part B of the survey form collected information about personal and family history of the persons in each household and consisted of 6 sections.

Part C collected anthropometric information about the individual persons and also lab reports were written in this section.

Anthropometric data included measurements of weight, height, waist and hip circumference. Participants were asked to wear light clothing and take off their shoes during anthropometry measurements. Height was measured to the nearest cm and weight to the nearest 0.1 Kg. Weight was taken with a standardized scale and height with a standardized measuring stick. Waist circumference was measured as the mid point between the iliac crest and the lower margin of the ribs.

Blood pressure was take by a medical student or doctor at least twice with 20 minute intervals, after ensuring that at least 30 minutes had passed since tea or tobacco were last consumed. A third BP measurement was taken if one or both of the first two readings were above the cutoffs for a diagnosis of hypertension.

2.5.2 Karachi City

2.5.2.1 Study protocol

This was a randomized clinical trial (RCT) conducted in subjects over 30 years of age who were diagnosed as having IGT according to World health Organization criteria (38). The IGT subjects were followed for a period of 18 months prospectively. Awareness about the primary prevention program was disseminated through posters\banners and leaflets. Our primary prevention team also visited different primary health care centres in the city to generate awareness about our primary prevention program and held diabetes screening camps at various public places such as parks and community halls.

To identify subjects from the general population who may be at increased risk of developing type 2 diabetes, a questionnaire was asked to be filled in as the first step. This standardized questionnaire asking about family history (parents or siblings with diabetes), high body mass index, low physical activity, age > 40 years, hypertension, high cholesterol or triglycerides and history of gestational diabetes or baby weighing > 3.5 Kg at birth was used to identify high risk subjects at this initial step. Those identified as high risk were further asked to undertake an Oral Glucose Tolerance Test (OGTT). Those subjects identified as

being IGT were stratified randomly by age into three different arms to ensure equal age representation in all the arms of the intervention. The age stratification was 31- 40 years, 41–50 years, 51–60 years and > 60 years into each of the three groups.

2.5.2.2 Recruitment and Questionnaire

A number of strategies starting with opportunistic screening at the 2 health care centres involved in the study was initiated. With the aim to reach a greater audience our diabetes prevention team arranged a series of 2-days awareness lectures at various places in the city by going to offices, service organizations, work factories and visiting health care centres. Lectures on diabetes and its prevention were delivered by the diabetes prevention team in local language to the audience on the first day. The audience were asked to fill in the risk questionnaire at the end of the first day. On the second day, screening of high risk subjects was done according to results of the questionnaire and all high risk subjects were invited for an OGTT.

During the time that the OGTT was done, all subjects underwent a detailed anthropometric and medical examination as well as been asked questions about their socio-demographic, physical activities and dietary habits including information on quantity and quality of meals by a dietician and physical trainer. Weight, height, waist circumference and blood pressure were measured at each scheduled visit. Weight and height was measured with the subjects minimally clothed, without shoes, in a standing position. Waist circumference was measured at the mid-point between the iliac crest and the costal arch. Blood pressure was measured twice, 5 min apart, in a sitting position, and the average of the two was recorded.

2.5.2.3 Intervention and Randomization

All subjects who agreed to participate in the study were randomized into three groups. First group (Control Group) was given standard medical advice, second group (ILSM Group) was given intensive lifestyle modification advice while thrid group (ILSM+Drug Group) was given intensive lifestyle modification advice and metformin 500 mg twice daily. The subjects assigned to their respective groups were followed till the close of the study.

The subjects in the control group were given general diet and exercise information at baseline and followed at subsequent visits but no specific individual counselling was done. The subjects in the intervention+drug group were given detailed advice about how to achieve the intervention goals, which included reducing > 5 % of body weight loss via diet control and physical exercise, total fat intake less than 30% of energy consumed, fiber intake of 15g/1000 kcal, and moderate exercise for minimum 30 min/day. Frequent ingestion of wholemeal products, vegetables and fruits, low-fat milk and meat products, and vegetable oils rich in monounsaturated fatty acids was recommended. The subjects had sessions with

a dietician and physical trainer at each visit and they were individually guided and encouraged to increase their level of physical activity. Endurance exercises such as walking, jogging and cycling were recommended to increase fitness. Supervised, progressive and individually tailored training advice was also offered to improve the functional capacity and endurance of each individual. These interventions were based on reinforcing behaviour modification via diet change and encouraging physical activity of each subject individually. The subjects in the intervention+drug group were seen every 2 months by a medical doctor for their drug adherence apart from the intervention advice.

2.5.2.4 Follow-up

Reinforcement and counselling was done every 2 months in the intensive and intensive+drug groups with visits to the medical officer, dietician and physical trainer. While every 3 months the subjects in the control group were seen by the medical officer.

2.5.2.5 Primary Outcome:

The primary outcome was defined as developing diabetes indicated by either fasting plasma glucose of (> 125 mg\dl) and \or 2-hours plasma glucose of (>199 mg\dl) during 9 and 18 months follow-up by an OGTT (38). Subjects identified as having diabetes were excluded from the study and given medical advice with referral to physicians for further follow-up.

2.6 Lab Investigations:

2.6.1 Blood and Urine Samples of Lyari Town Survey

Specimens were collected at home on Saturdays and Sundays by five mobile teams consisting of two phlebotomists each. At the time of blood collection, all participants were asked to provide consent for blood tests for fasting blood glucose and lipid profile and urine for proteinuria.

All blood samples were collected in two separate test tubes; a red cap vacutainer and green cap sodium fluoride tube. A total of 12 cc of blood was taken from each patient. 10 cc was place in the red vacutainer for analysis of Lipid profile and insulin serum levels and remaining 2cc was placed in the green NaF test tube for analysis of fasting glucose.

Within 1 hour of collection the blood was centrifuged and separated. Tests were done by the Vitalab Selectra Analyzer for Glucose, Cholesterol, Triglycerides, HDL-Cholesterol, LDL-Cholesterol and Insulin levels. Fasting blood glucose and lipid profile were done by GOD PAP method and CHOD PAP method respectively. Insulin levels were done by Elisa method.

Urine samples were collected from the respective subject on the morning of collection. They were advised to keep the specimen in a cool and shaded area. Urine tests included a

qualitative determination of proteinuria and a quantitative measurement of microalbuminuria.

2.6.2 Samples of Karachi City

All IGT subjects in the primary prevention study had fasting lipid profile, fasting insulin levels, OGTT and HbA1c done at 0, 9 and 18 months. At the interim 9-month visits, confirmation of diabetes was made with OGTT. Plasma glucose was measured using the glucose oxidase–peroxidase method. The fasting serum lipid profile was estimated using standard enzymatic procedures. HbA1c was measured by HPLC using Biorad, a procedure certified by the National Glycohemoglobin Standardization Program.

2.7 Statistical analysis

2.7.1 Lyari Data

All data was recorded on forms developed using TeleForm® Version 6.01, an optical character recognition software. Forms were scanned and verified using TeleForm® Version 6.01 and exported into an SQL database. Later this data was converted into the software package SPSS version 11.5 (Statistical Package for Social Sciences) for analysis.

The main variables for analysis included age, gender, socioeconomic and ethnic groups, fasting glucose and insulin levels, lipid profile, proteinuria and microalbuminuria, hypertension, body mass index, waist-hip ratio, mid-abdominal circumference, smoking exposure and family history of disease. Some of the other risk factors to be included in the analysis were physical activity and diet.

The prevalence of metabolic syndrome was determined by simple percentages and with 95% confi dence intervals (CIs). For group comparisons, the chi-square test was performed; the Student t-test was performed for continuous variables. A P value of <0.05 was considered statistically significant. The age-specific distribution of prevalence of metabolic syndrome was calculated for men and women separately and described in percentages. A kappa test was done to examine the agreement among the defi nitions. All P values presented are two tailed (Paper 1).

2.7.1.1 Dietary data:

Dietary consumption was assessed by a 33 food items interviewer-administered semi quantitative food-frequency questionnaire in the lyari town study. The food items were categorized into 6 major food groups: Dairy, meat, fat and sweet, cereals, vegetables and fruits groups. Out of the 363 subjects assessed for metabolic syndrome 362 completed the food-frequency questionnaire.

We used cluster analysis to identify dietary patterns and to segregate subjects based on the similarity of diet. We chose food variables because we wanted to identify food patterns clusters. K-means cluster analysis was used to define clusters of subjects using the cluster analysis option in SPSS. This procedure attempts to identify relatively homogeneous groups of cases based on selected characteristics.

In K-means cluster analysis, the homogeneity of cases within a cluster is measured by the total within-cluster sum of squares. Cluster memberships are determined by sequentially moving cases from one cluster to another so that the total within-cluster sum of squares is minimized. The algorithm requires the number of clusters to be specified prior to analysis. It is possible to identify seeds using information derived from previous research. Five clusters were defined and we investigated metabolic syndrome prevalence in each cluster and compared the dietary patterns of the clusters with the lowest and highest prevalence of metabolic syndrome (Paper 2).

2.7.1.2 Assessing insulin resistance

Insulin resistance was assessed in 227 normal subjects by calculating HOMA, QUICKI and McAuley Index indices by the following calculations:

- HOMA-R = Insulin (Iu/ml) × glucose (mmol/l)/22.5
- QUICKI = 1/ [log (fasting insulin) + log (fasting glucose)]
- McAuley Index = Exp [2.63-028 ln (Insulin in Mu/l)-0.31ln (triglyceride in mmol/l).

Characteristics of the subjects according to gender were analyzed using an independent sample t-test. Data was presented as quartiles of fasting insulin, HOMA-IR, QUICKI and McAuley index to observe the various percentiles of insulin sensitivity and determine insulin resistance according to defined standard protocols. The statistical analysis was conducted using SPSS for Windows (version13, SPSS Inc., Chicago, IL, U.S.A.), and $p < 0.05$ was considered statistically significant (Paper 3).

2.7.2 Primary Prevention Study

Mean and standard deviation are reported for continuous variables and inter-group comparisons were tested by two tailed ANOVA in this study. Comparison of proportions was by chi square analysis. The proportion of subjects developing diabetes in each group and their comparison was also done by chi square analysis.

For the intervention measures, the absolute and relative risk reductions and 95% CIs of the estimates and the number needed to treat to prevent diabetes in one person were calculated. A p value <0.05 was considered significant. The statistical package SPSS (PASW Statistics 18) was used for analyses (Paper 4).

2.8 Ethical Considerations

2.8.1 Ethical Clearance

The study protocols of the epidemiological survey in Lyari Town and the Primary prevention study in Karachi city were approved by the institutional review board of the Baqai Institute of Diabetology and Endocrinology (BIDE).

The study protocols had also been sent to the Norwegian Ethics Committee for approval.

2.8.2 Informed Consent

Informed consent is a prerequisite for all research involving human subjects. Verbally and in writing, subjects were informed about the purpose and scope of both the studies independently, the benefits and risks of the studies, how the results will be used and reported and the method of confidentiality that will be used in reports. Since all the subjects were interviewed from a structured questionnaire; questions did not probably change from subject to subject.

All participants in both the studies were required to give their informed consent voluntarily and the study was carried out in accordance with the Declaration of Helsinki as revised in 2000.

All participants reserved the right to withdraw from the study at any time, even if they have previously given consent to be part of study. The findings were treated with highest possible degree of confidentiality. Each subject was given a unique identity number.

After data collection was completed and the subjects had received their results the data was anonymized. Names were deleted and the data could not be traced back to any specific individual.

3 Results

3.1 Synopsis of Paper 1

Reference:

Prevalence of Metabolic Syndrome in Urban Pakistan (Karachi): Comparison of Newly Proposed International Diabetes Federation and Modified Adult Treatment Panel III Criteria. M. Zafar Iqbal Hydrie, A. Samad Shera, Asher Fawwad, Abdul Basit and Akhtar Hussain. METABOLIC SYNDROME AND RELATED DISORDERS, Volume 7, Number 2, 2009.

Title: Prevalence of Metabolic Syndrome in Urban Pakistan (Karachi): Comparison of Newly Proposed International Diabetes Federation and Modified Adult Treatment Panel III Criteria

Abstract:

The clustering of central obesity, dyslipidemia, hypertension, and hyperglycemia known as metabolic syndrome has been associated with a two- to three-fold increase in type 2 diabetes (T2DM) and cardiovascular disease (CVD). It is recognized that the features of the metabolic syndrome can be present 10 years preceding T2DM and CVD. The objective of our study was to determine the prevalence of metabolic syndrome in adults aged 25 years and older from an urban population of Karachi, Pakistan, according to the International Diabetes Federation (IDF) definition and modified Adult Treatment Panel III (ATP III) criteria. This study involved a survey conducted from July, 2004, to December, 2004, by generating a computerized random sample of households in Lyari Town using a geographical imaging system (GIS). Out of the 85,520 households, 532 households were randomly selected and 867 adults ≥25 years old consented to take part in the survey; 363 of these subjects gave blood samples. The prevalence of diabetes was 9.4%, whereas 5.6% had impaired fasting glucose (abnormal glucose tolerance 15%). The prevalence of metabolic syndrome according to the IDF definition and modified ATP III criteria was 34.8% and 49%, respectively. Inclusion of modified waist circumference and specifi c body mass index (BMI) cut offs for Asians may help predict metabolic syndrome at an early stage. High prevalence of metabolic syndrome was identified irrespective of the definition applied in this population. This may call for immediate action to halt the accelerating risk of diabetes and CVD that would lead to a possible unparalleled rise in the cost of health care and human suffering.

3.2 Synopsis of Paper 2

Reference:

Dietary Patterns Associated with Risk for Metabolic Syndrome in Urban Community of Karachi Defined by Cluster Analysis.

M. Zafar Iqbal Hydrie, Abdul Basit, A. Samad Shera, Rubina Hakeem and Akhtar Hussain.

Pakistan Journal of Nutrition 9 (1): 93-99, 2010. ISSN 1680-5194.

Title: Dietary Patterns Associated with Risk for Metabolic Syndrome in Urban Community of Karachi Defined by Cluster Analysis.

Abstract: Dietary trends have been found to be related with metabolic syndrome in various studies. To identify dietary patterns and study associations between the dietary patterns of subjects with high and low risk of metabolic syndrome in a Karachi population. A group of 871 men and women were selected randomly from 532 households. Data about consumption of specific foods was available for 867 adults. Participants completed a health and lifestyle questionnaire and 363 subjects provided fasting blood samples for glucose and lipids. Dietary intake was assessed by a questionnaire to identify consumption of 33 specific food items and the dietary patterns categorized into 6 food groups was assessed by cluster analysis. Five dietary patterns were identified through cluster analysis. Cluster 1 had the lowest proportion of persons with metabolic syndrome i.e. 42.7% while cluster 2 had the highest percentage of metabolic syndrome subjects (56.3%) ($p = 0.09$). Consumption of fat and caloric dense foods was significantly higher among highest risk group (cluster 2) compared to lowest risk group (cluster 1) ($p = 0.0001$). The consumption of food groups containing fruit, milk and meat was also more than twice in high risk compared to low risk group ($p = 0.0001$). Even within the same population there are marked differences in dietary patterns and these apparently contribute to the risk of developing metabolic syndrome. Dietary pattern studies will help elucidate links between diet and disease and contribute to developing healthy eating guidelines.

3.3 Synopsis of Paper 3

Reference:

Detecting Insulin Resistance in Pakistani Subjects by Fasting Blood Samples.

M. Zafar Iqbal Hydrie, Abdul Basit, Asher Fawwad, Muhammad Yakoob Ahmedani, A Samad Shera and Akhtar Hussain.

Accepted in The Open Diabetes Journal.

Title: Detecting Insulin Resistance in Pakistani Subjects by Fasting Blood Samples

ABSTRACT:

Background: Insulin Resistance has been identified as an independent risk factor for a number of chronic diseases such as diabetes and cardiovascular diseases (CVD).

Objective : To identify a simple indirect method for detecting insulin resistance (IR) in our population.

Methods: Geographical Imaging Systems (GIS) was used for randomly selecting the subjects. For visiting the 532 households selected by GIS, 9 field teams were developed. A total of 871 subjects older than 25 years were approached by these teams out of which 867 agreed to participate in the survey. IR was assessed in 227 normal subjects by fasting insulin, HOMA-IR, QUICKI and McAuley Index.

Results: IR was defined at 75th percentile cut off of insulin levels (9.25 U/mL) and HOMA-IR (1.82). The 25th percentile cut off was used for defining IR in QUICKI (0.347) and McAuley Index (6.77).

Conclusion: A common approach towards managing subjects with metabolic risk factors will help identify IR earlier and using IR reference values identified from simple indirect methods would be of value in such cases. However larger population based studies are needed to further define and validate these cutoff values for insulin resistance.

3.4 Synopsis of Paper 4

Reference:

Effect of intervention in subjects with high risk of Diabetes Mellitus in Pakistan.

M. Zafar Iqbal Hydrie, Abdul Basit, A Samad Shera and Akhtar Hussain.

To be submitted.

Title: Effect of intervention in subjects with high risk of Diabetes Mellitus in Pakistan.

Abstract:

Aims: The aim of the study was to observe the rate of conversion from impaired glucose tolerance (IGT) to diabetes following lifestyle modification program and a combination of lifestyle modification and oral hypoglycaemic agent (metformin) compared to a control population with 18 months follow up.

Methods: Around 40 screening camps were organized following a series of awareness lectures at various places in the city. Nearly 5000 people attended these lectures offices, organizations, factories, health care centres and visited the screening camps. Around 1825 subjects over 30 years of age were identified as high risk on the basis of a questionairre and requested to undertake an oral glucose tolerance test (OGTT). Out of these1739 subjects took the OGTT and 317 subjects were identified as having impaired glucose tolerance (IGT). They were randomized into three groups. First group was given standard medical advice (Control Group), second group was given intensive lifestyle modification advice (LSM Group) while third group was given intensive lifestyle modification advice and metformin 500mg twice daily (LSM+Drug Group).

Results: At the end of the study 273 subjects completed the study giving a compliance rate of 86%. A total of 47 incident cases of diabetes were diagnosed during the study. The overall incidence of diabetes was 4 cases per 1000 person-months with the incidence of diabetes as 8.6 cases in the control group, 2.5 cases in the Life Style Modification (LSM) group and 2.3 cases in the LSM+drug group.

Conclusions: This study showed that lifestyle intervention had a major impact in preventing diabetes among IGT subjects in this region. However, addition of drug in the intervention did not show any improved results. Resource constrain societies are challenged with the additional burden of diabetes cost on their already ailing economy. Therefore, we recommend that lifestyle modification advice and follow-up should be incorporated in primary health care.

3.5 Summary of the Results

In the epidemiological survey of lyari the overall prevalence of metabolic syndrome was 34.8% and 49% according to IDF and modified ATP III classifications respectively (Table 9).

Tabell 9: Prevalence and 95 % CI of MS using modified ATP III and IDF definition by age and sex.

Age group	n	ATP III % (95%CI)	IDF % (95%CI)
Overall	**363**	**49 (43.8 - 54.1)**	**34.8 (29.65 -39.94)**
Male			
25 – 34	37	54.1 (37.98-70.21)	31.3 (15.18-47.41)
35 – 44	30	56.7 (38.8-74.59)	21.4 3.50-39.29)
45 – 54	15	53.3 (27.99-78.6)	46.7 (21.39-72.00)
> 55	35	57.2 (40.80-73.6)	34.4 (18.66-50.13)
Total	117	55.6 (46.53-64.66)	31.8 (22.73-40.86)
Female			
25 - 34	107	27.1 (17.62-36.57)	14.9 (5.42-24.37)
35 - 44	68	51.5 (39.61-63.38)	37.3 (25.41-49.18)
45 - 54	31	58.1 (40.49-78.7)	60.0 (42.39-77.6)
> 55	40	76.8 (63.71-89.88)	69.05 (54.72-83.37)
Total	246	45.9 (39.65-52.14)	36.1 (29.85-42.34)

The prevalence rates of the metabolic syndrome increased with increasing age. Significant differences in the prevalence of metabolic syndrome with respect to age groups were found only in females (P values <0.05) (Table 9). Fairly good agreement between the two definitions of metabolic syndrome was seen with a kappa value of 0.67. All of those (n = 120) who were classified as having metabolic syndrome following IDF criteria were sustained according to the modified ATP III criteria.

Female subjects were younger, but had higher BMI values and total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) levels compared to males. Males were older, had higher waist circumference, blood pressure and triglyceride values. Overall 30% of the subjects had higher total cholesterol, triglycerides, and LDL levels, as shown in Table 10.

Tabell 10: Percentage of biochemical risk factors for Metabolic Syndrome

Variable	**Males n (%) 95 %CI**	**Female n (%) 95% CI**	**Total n (%) 95 %CI**
Cholesterol > 200 mg/dl	26/95 (26.8%) (17.9 - 35.6)	68/216 (31.5%) (25.3 - 37.7)	94/313 (30.0%) (24.9 - 54.9)
Triglycerides > 150 mg/dl	35/94 (37.2%) (27.6 - 47.0)	57/208 (27.4%) (21.3 - 33.5)	92/302 (30.5%) (25.3 - 55.8)
Low Density Lipoprotein (LDL) >130 mg/dl	25 / 97 (25.8%) (17.1 - 34.5)	63 / 216 (29.2%) (64.8 - 35.2)	88 / 313 (28.1%) (23.1 - 51.2)
High Density Lipoprotein (HDL) < 40 mg/dl for males & < 50 mg/dl for females	63 / 96 (65.6%) (56.1 - 75.1)	153 / 216 (70.8%) (64.8 - 76.9)	216 / 312 (69.2%) (64.1 - 133.3)

Around 70% had low HDL levels, which is similar to that found in South Asian subjects residing in Europe (53). The prevalence of diabetes was found to be 9.4%, while 5.6% had impaired fasting glucose (Total abnormal glucose tolerance around 15%).

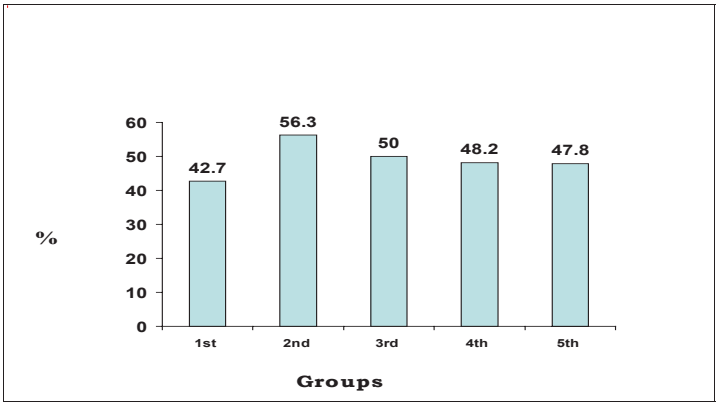
We used cluster analysis to look at the diet data of the Lyari epidemiological survey and we identified five distinct groups in this population on the basis of cluster analysis. A total of 75 subjects (20.7%) were in cluster one, 71(19.6%) in cluster two, 64(17.8%) in cluster three, 85 (23.5%) in cluster four and 67 (18.5%) in cluster five. Frequency of consumption of each food group in all the clusters is shown in Table 11.

Tabell 11: Frequency of Consumption of food groups in Clusters

	Clusters				
	1	2	3	4	5
milk group	24	69	32	57	29
meat group	35	79	61	61	56
fat group	13	70	20	42	44
cereal group	76	91	90	92	81
vegetables group	72	94	83	93	82
fruit group	34	74	45	59	46

While looking for the proportion of subjects with metabolic syndrome in each cluster we observed that cluster one had the lowest while cluster two had the highest percentage of subjects with the metabolic syndrome (42.7% vs. 56.3%), with a p value of 0.09 as shown in Figure 8.

Figur 8: Metabolic syndrome in five Clusters according to Modified ATP III Definition



The dietary pattern in cluster 2 was loaded with both healthy (milk, legumes, vegetables and fruits) and unhealthy (refined grains, potatoes, meat and meat products , high fat dairy products, snacks, sweet items and fruit juices) foods. Although healthy foods are reported to be protective against the metabolic syndrome, the cluster's unhealthy diet constituents had adverse effects on the metabolic markers which might have lead to the increased prevalence of metabolic syndrome as seen in this study.

For analyzing the insulin resistance cutoff values, only those subjects with a fasting blood glucose of < 100 mg/dl were included to ensure that our study population only had normal glucose tolerance subjects. A total of 227 normoglycemic subjects (70 men and 157 women) were selected from the Iyari epidemiological survey. General characteristics of this group of subjects are shown in Table 12.

Tabell 12: General characteristics of the study subjects

Subject	Male n = (70) Mean ± SD	Female n = (157) Mean ± SD	Total n = (227) Mean ± SD
Age (years)*	43.10 ± 12.95	36.87 ± 11.40	38.79 ± 12.21
Body Mass Index (kg/m^2) **	22.35 ± 4.10	25.09 ± 6.27	24.27 ± 6.07
Waist Circumference (cm)	87.42 ± 12.84	85.31 ± 14.09	85.96 ± 13.72
Systolic Blood Pressure (mmHg)	127.94 ± 19.95	121.73 ± 17.14	123.59 ± 19.55
Diastolic Blood Pressure (mmHg)*	84.70 ± 12.11	77.70 ± 12.87	79.79 ± 13.02
Cholesterol (mg/dl)	175.06 ± 44.02	178.72 ± 44.85	177.61 ± 44.53
Triglyceride (mg/dl)***	160.58 ± 123.27	128.90 ± 66.33	138.39 ± 88.25
Low Density Lipoprotein (mg/dl)	108.22 ± 30.15	114.48 ± 32.56	112.59 ± 31.91
High Density Lipoprotein (mg/dl)***	38.65 ± 11.52	43.48 ± 12.52	42.04 ± 12.40
Glucose (mg/dl)	80.80 ± 8.82	79.94 ± 10.63	80.21 ± 10.10
Insulin (µU/mL)	7.60 ± 2.78	8.40 ± 4.50	8.15 ± 4.05
HOMA	1.48 ± 0.58	1.61 ± 0.90	1.57 ± 0.81
QUICKI	0.36 ± 0.02	0.36 ± 0.03	0.36 ± 0.03
McAuley	7.09 ± 1.33	7.37 ± 1.48	7.29 ± 1.44

* P-value < 0.001 ** P-value < 0.005 *** P-value < 0.05

Females were significantly younger than males with lower waist circumference but higher Body Mass Index (BMI). Mean fasting insulin and HOMA-IR was also higher in females while other indices of insulin resistance were not much different in males and females.

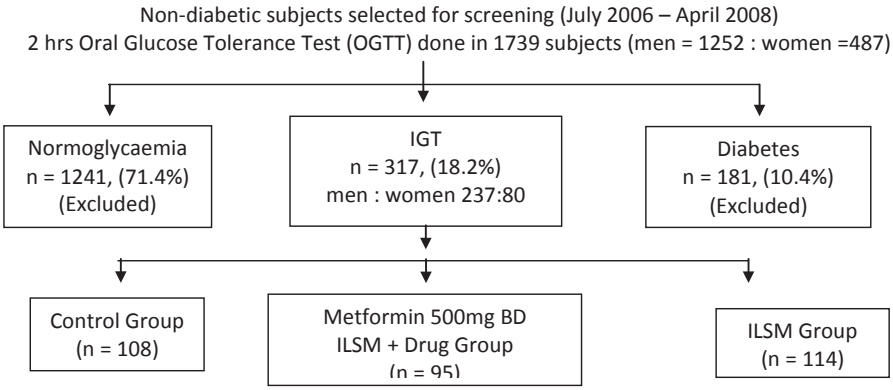
The 75th percentile cut off was used as a value for defining insulin resistance for fasting insulin levels (9.25 U/mL) and for HOMA-IR (1.82) while the 25th percentile was taken as cut off for defining insulin resistance according to QUICKI (0.347) and for McAuley Index (6.77) as shown in Table 13. These were taken as cutoff reference values for defining insulin resistance in the normal population.

Tabell 13: Quartiles of fasting serum insulin, HOMA-IR, QUICKI and McAuley Index.

	P25	P50	P75
Insulin	5.95	7.8	**9.25**
HOMA-IR	1.087	1.454	**1.823**
QUICKI	0.347	0.359	**0.376**
McAuley Index	**6.77**	**7.046**	**7.33**

In the second study which was the primary prevention program, an estimated 5000 people attended the diabetes prevention lectures and visited the screening camps. Around 2300 people filled in the high risk questionnaire. Around 1825 were identified as high risk and 1739 of these subjects agreed to undertake a standardized oral glucose tolerance test (OGTT).

Figur 9: Flowchart with recruitment of persons for the oral glucose tolerance test (OGTT) and screening and randomisation.



Of the 1739 subjects undergoing OGTT, the majority (72%) were males; while 10.4% were found to have diabetes while 18% were having impaired glucose tolerance (IGT). The baseline characteristics of the 1739 subjects showed an increasing trend of age, BMI, and blood pressure from NGT to DM as shown in table 14 below.

Tabell 14: Baseline Characterstics of 1739 identified high risk subjects by questionnaire

	NGT	IGT	DM	p-value
N	1241	317	181	
Age of patient (years)	40.1 ± 8.9	43.6 ± 9.9	44.4 ± 9.7	<0.0001
Body Mass Index (kg\m^2)	25.8 ± 5.3	27.1 ± 5.0	27.3 ± 5.2	<0.0001
Systolic BP (mmHg)	118.3 ± 16.5	121.5 ± 16.8	124.3 ± 17.7	<0.0001
Diastolic BP(mmHg)	82.5 ± 11.0	84.6 ± 10.9	85.4 ± 13.1	0,001

The 317 IGT subjects were randomized into three groups is shown in table 15. More than half (56%) of the subjects were young between 30-44 years of age in this IGT cohort. Positive family history of diabetes, hypertension, cardiovascular disease and stroke was present in 49%, 38%, 31% and 17% of the subjects while 25% had hypertension at start of study.

Tabell 15: Baseline anthropometric and biochemical characteristics of the Randomized Groups

	Control	Lifestyle	Lifestyle+ Met
N	108	114	95
Age in years	44.2 ± 10.9	43.1 ± 10.1	43.5 ± 8.4
Body Mass Index (kg\m^2)*	27.0 ± 5.7	26.1 ± 4.7	28.1 ± 4.3
Systolic BP (mmHg)	121 ± 17	123 ± 19	120 ± 14
Diastolic BP(mmHg)	84 ± 11	86 ± 12	84 ± 9
Cholesterol (mg/dl)	179.1 ± 37	178.6 ± 34	180.0 ± 36
Triglycerides (mg/dl)	153.4 ± 109	147.3 ± 86	171.5 ± 119
HDL-C (mg/dl)*	37.8 ± 4.3	37.4 ± 4.5	37.8 ± 7.8
LDL-C (mg/dl)	117.2 ± 25.1	116.5 ± 22.7	117.0 ± 24.6

At the end of the study 273 subjects completed the study giving a response rate of 86%. A total of 47 incident cases of diabetes were diagnosed during the study; 19 cases at 9 months and 28 cases at 18 months or closure of the study. The incidence of diabetes was 8.6 cases in the control group, 2.5 cases in the Life Style Modification (LSM) group and 2.3 cases per 1000 person-months in the LSM+drug group as shown in table 16. The numbers to be treated to prevent one incident case of diabetes was 9 and 8 in lifestyle and LSM+Drug groups respectively.

The absolute and relative risk reduction was also significantly lower in the lifestyle and ILSM+Drug groups compared to control group. The numbers to be treated to prevent one incident case of diabetes was 9 and 8 in lifestyle and ILSM+Drug groups.

Tabell 16: Comparision of the outcome at 18 months in the four groups

	Control	Lifestyle	Lifestyle+ Met
n	82	107	85
cases per 1000 person-months	8.6	2.5	2.3
Absolute risk reduction %		10.7	11.5
Relative risk reduction % (95% CI)		71(13.7-90.3)	76.5(19.7-93.1)
NNT for 18 months to prevent DM in one case		9	8

4 Discussion

4.1 Methological Issues

4.1.1 Choice of Study design

We undertook two studies and we had two separate study designs for them. A cross sectional design was chosen for the first study which was an epidemiological survey. Cross sectional studies are done for determining the prevalence of a disease and to study the association of risk factors with the occurrence of disease. The aim is to describe individuals in the population at a particular point in time and their history of exposure at that time. Cross sectional studies do not present clear evidence on the relationship between risk factors and disease since both are measured at the same time, making it difficult to determine whether the risk factors are truly risk factors for the outcome or if they are influenced by the outcome. However in terms of chronic diseases such as diabetes where the causation of disease has been fairly well established, data from cross sectional survey helps to develop or strengthen the hypothesis about the related risk factors. Thus this study design was used for our survey as has also been done in majority of surveys to determine the prevalence of chronic diseases, both in Pakistan and in other countries (12,23,26-29). For our second study which was an intervention we used a randomized control trial (RCT) design to study the effect of intervention in subjects with high risk of developing type 2 diabetes. We had three arms or groups with two intervention groups and one control group. The groups had to be randomly selected from the target population, in this case IGT subjects who had taken an OGTT. Similarity between the groups was needed to ensure that the only difference between them at the outcome would be the effect of intervention we are trying to observe. For this purpose we stratified the groups according to age to ensure similar age distribution between the subjects in all the groups. Since the intervention included counselling and motivating the subjects for lifestyle modification it could not be blinded as a drug and placebo trial and the subjects as well as the researchers knew which individual was enrolled in which group. This study design has been used in studies to observe the effect of intervention of subjects at risk of developing diabetes (82).

4.1.2 Sample size

For the lyari study we assumed that the lower limit prevalence of T2DM to be 11% in this population. The size of the population from which the study sample was to be selected (persons 25 years and older in Lyari Town) was 244,000, the worst acceptable result would be ±1.5% from the true population value. Thus our study would require a sample of at least 713 individuals to have 80% power to detect the true population value. Based on the same

assumptions as used for T2DM (11%); hypertension (10% prevalence) and proteinuria (5%), our study would have 80% power to detect the true value in a sample size of 727 and 778, respectively.

If the sample size is insufficient, the statistical power would be low and we would not be able to detect an association even if it is present leading to β-error. The precision of the estimate would also be low. In the field we were able to interview more than the required sample size (n = 867) but people's reluctance to have the blood tests left us with less than the desired sample size (n = 363) at the end of the study. However since the prevalence of metabolic syndrome is between 30 -45% in the general population the sample size enabled us to analysis and interprets the results on most of the occasions.

For the intervention study nearly 2000 suspected high risk cases identified by a high risk questionnaire were to be invited to participate. Considering 30% IGT cases in the high risk individuals around 600 would likely to have IGT. The IGT cases will be randomly allocated on three different arms, two preventive groups and one control group, all with 200 participants. With an expected conversion rate of nearly 30% T2DM in the control group (n = 60) and an reduction of 15-20 % in the intervention group (n = 9 -12) the sample size will be adequate considering ß = 0.20 and α = 0.05.

4.1.3 Error

Systemic error that modifies the result towards one direction is called bias. While random error does not influence the results in only one direction, the effects of random error can go either of the two ways. If a sample is large enough, the effect of random error will be balanced. Type 1 error occurs when data leads us to believe that something is true when in reality it is not. While type 2 error occurs when data leads us to believe that the null hypothesis is not rejected, when in reality it is.

4.2 Bias

4.2.1 Selection bias

Systematic introduction of error may occur during subject selection for the study and is termed selection bias. This occurs when inclusion into a study is influenced by the characteristics of the subjects which might also affect the outcome. By using a random selection procedure we can minimize the selection bias by giving everybody the equal chance to be selected. According to statistical point of view all observational studies have built in bias but the challenge is to interpret how they affect the outcome of the research.

In our epidemiological study in Lyari, we recruited subjects by using Geographical Information System (GIS). Lyari Town Geographical Information System was made by Population Census Office, Statistics Bureau Sindh and National Database and Registration Authority (NADRA) to define the geopolitical boundaries and population density of Lyari Town (estimated 2004 population of 700,000). A year-long, detailed physical survey of Lyari Town was undertaken using available plot maps. All household structures were given a unique identification number, along with all health, education and other civic facilities available to its residents. The new maps were finally digitized using a geo-referenced satellite image of Lyari town. The Lyari Town GIS was used to assess indicators that may be of interest to researchers, such as determining the community-based prevalence of chronic diseases among adults as has been done by our group. Computerized random selection of households by GIS removes the selection bias to an extend as we visited the specified households instead of setting a camp in the locality to invite participants. Although we had over representation of women since the survey was done on weekdays compared to males as most of the men went to work on weekdays and were not home at the time of the survey.

As for our intervention study, the IGT subjects were selected on the basis of the OGTT results. This made selection specific to high risk subjects and we tried to ensure that all the subjects in the groups had similar baseline characteristics. For this purpose we stratified them according to age to try to ensure that all subjects had similar characteristics and ages in all the groups.

4.2.2 Information bias

Systematic error in collecting information from the subjects is termed information bias. By asking questions differently and interpreting or coding information in different ways could lead to information bias. In both our studies, all the team members and the field workers were trained before the start of the studies as regards filling the questionnaires as well as been checked periodically during the study to ensure that proper data entries were been done according to protocol. The field workers in the epidemiological survey were from the local community and they knew the local dialect and had an understanding of the cultural norms. While for the intervention study the same prevention team followed all the subjects to ensure the same quality of care and understanding throughout the study.

4.2.3 Measurement bias

Since most of the survey form was in a structured interview questionnaire and subject to response by participants, if a question was not answered a variable would be missing in the

final analysis. Thus variables had missing data in the interview section of the questionnaire if the answer was not given.

As regards the anthropometry measurements certification course was arranged for the field team of the lyari study for measuring height, weight and blood pressure at the National Institute of Cardiovascular Diseases while for the intervention study it was done by health professionals.

4.3 Confounding

Confounding refers to the issue when a part of or the entire effect of a variable is influenced by another supposedly causal variable. Controlling for confounding can be done either by multivariate analysis or stratifying the data. In our epidemiological study we tried minimizing confounding by using randomized computer based selection of the households and study subjects. The effect of age and gender was minimized by doing stratified analysis. However, some confounders might have not been controlled due to lack of data collection, for example the diet section which was not very extensively covered in the form. In the intervention study confounding between the groups was controlled by stratifying by age during the randomization phase to ensure similar baseline characteristics in all subjects.

4.4 Internal validity

If the results of a study are true for those who participated in the study, the results are considered internally valid.

Internal validity is increased by reducing bias and controlling for confounding. We tried to secure the internal validity of the survey by reducing the confounding effects and measurement bias as mentioned above. To reduce confounding we also stratified some of the results for age and gender where appropriate.

4.5 External validity

In terms of generalization or external validity the findings of this study reflected the scenario of urban Population. Lyari was chosen as it is one of the oldest, most densely populated part of the city with its residents having a diverse community representing every ethnic group found in Pakistan. The sex ratio was similar as for the country (male/female ratio of 1.034 males for lyari vs.1.045 males for the country). The mean age for males in lyari was 23.5 vs. 20.7 years for the country while for females it was 24.5 in lyari vs. 21 years for the country; suggesting similar age and gender distribution for both populations. Given this we believe that the findings of the study can be inferred on the general population and is more likely to be externally valid for the population of Pakistan.

As regards the intervention study this was a selected high risk IGT group which can be compared with the same high risk population of Pakistan.

4.6 Strengths of the study

Lyari Town Geographical Information System was made to dynamically link the national census database to a purpose built geographical information system (GIS) to define the geopolitical boundaries and population density of Lyari Town. We generated a computerized random sample of 532 households from among the 85,520 households in Lyari Town. There were 11 union councils or subdivisions of Lyari Town where the samples were taken from ensuring that each union council had equal opportunity to be represented in the sample selection. We expected approximately 1000 adult men and women above 24 years of age in the selected households in Lyari. If members of a household that had been selected refused to consent to household interviews, we followed a predefined protocol until we had enrolled a household from the neighbourhood of the original household selected.

Individual members within households also reserved the right to refuse participation in the study. Assuming a 10% refusal rate (by members within the household at the time of interview) and another 20% refusal rate by those who decline to provide consent for a blood test, we expected at least 854 individuals to participate in this study.

As for the intervention study, this was from a high risk population which was selected based on the results of the OGTT. Thus we had certain criteria for selection of subjects for the study and we also tried to ensure uniformity within all the groups by stratifying for age in all groups.

4.7 Limitations of the study

Looking at the limitations of the study, the study design was cross sectional for the epidemiological research survey, which is not the ideal design as cross sectional studies do not present clear evidence on the relationship between risk factors and disease since both are measured at the same time, making it difficult to determine whether the risk factors are true factors for the outcome or if they are influenced by the outcome themselves. Also despite being randomized by computer based GIS it was conducted in one selected area of the city and had low number of subjects in the final analysis making us to state that the results of the survey which is urban based needs to be interpreted with caution when generalizing for the whole population of Pakistan.

As regards the prospective intervention study it was difficult to evaluate the compliance of all the subjects during the follow up period. The specific target goals were recorded but the

diet and physical activity diaries were based on participants recall and subjective in nature. The comprehensive follow up of the participants was made more difficult by the participants being aware of their glycaemic status and maybe discussing this with other health professionals.

4.8 Discussion of the main results

The objective of the epidemiological study was to determine the prevalence of metabolic syndrome and related risk factors in a representative sample of 25 years and older adults from an urban population of Karachi. This study also helped to define some baseline values for insulin levels in the normal population and try to assess insulin resistance which is a new entity in Pakistan. This also helped to lay the foundation for the second study by showing the poor dietary habits of our population and the need to have a intervention program in our population; and thus leading to a intervention trial of primary prevention of Type 2 diabetes.

4.8.1 Prevalence of Abnormal Glucose Tolerance

The overall prevalence of abnormal glucose tolerance was 15% in our lyari epidemiological study, with the prevalence of diabetes to be 9.4%. The national survey conducted by the Diabetic Association of Pakistan (DAP) in collaboration with the World Health Organization (WHO) during the 1990s reported 11% prevalence of type 2 diabetes, with an overall abnormal glucose tolerance of 22% (26–29). Conducted in both urban and rural areas of all the four provinces of Pakistan, the national survey used WHO guidelines for the diagnosis of T2DM and impaired glucose tolerance (IGT) in over 5,600 persons 25 years and older while we used only the fasting criteria. By doing OGTT we might have yielded a higher prevalence of abnormal glucose tolerance since more cases of IGT compared to 5.6% of IFG cases might have been reported. Nearly 72% of the newly diagnosed subjects did not know they had diabetes before the survey, a finding reported also in the national survey (12,26). The mean age was highest in the subjects with diabetes followed by IFG and than normal population, also seen in the national survey (26-29).

4.8.2 Prevalence of Metabolic syndrome – Different Definitions

The prevalence of metabolic syndrome ranged from 8.2– 49% according to the definition used in this survey. The prevalence of Metabolic Syndrome according to WHO and EGIR criteria was low as compared to the other definitions probably due to both definitions using a two stage screening process. Thus fewer subjects were classified as having the metabolic syndrome. The percentage of subjects classified as having Metabolic Syndrome by ACE and IDF modified criteria for Asians was high, similar to as reported in other studies (57,67,68).

When stratified by gender the prevalence was 2-3 folds higher in females by most of the definitions, such as WHO definition (*6.9% for males; 13.9% for females*), by EGIR definition (*3.1% for males; 10.7% for females*) and by IDF definition (*31.8% for males; 36.1% for females*), while by modified ATP III it was more in males (*55.6% for males; 45.9% for females*).

Each component of the risk cluster defining metabolic syndrome has variability because of its regulation through genetic and acquired factors. The differences in the prevalence of the various component of the metabolic syndrome were because of the difference in the cut-off values used by the different definitions. The EGIR and ACE definitions did not include diabetes while ATP III, WHO and modified IDF definitions included diabetes and IGT as one of the components of MS. The EGIR in addition suggested fasting hyperinsulinemia (upper 25th percentile) as the necessary component of metabolic syndrome.

4.8.3 Prevalence of Metabolic syndrome according to modified ATP and IDF Definition

The prevalence rate was relatively higher following modified ATP III criteria in our study population. Other studies in the region have also showed high prevalence rates ranging from 35.2% to 41% (68,116). Our study showed an alarming prevalence of 49% of the metabolic syndrome in an urban Pakistani population according to modified ATP III criteria, whereas hospital-based studies have shown a prevalence of 44% using the original ATP III criteria (73,74,116). One reason for the observed higher rate of metabolic syndrome in this study might be the use of modified cut-off criteria for BMI in Asians (115). Our study is probably the first community-based study in an urban population on metabolic syndrome with modified ATP III definitions of metabolic syndrome. Our study also showed a prevalence of 34.8% of the metabolic syndrome according to the IDF definition compared to 26% in the Chennai Urban Rural Epidemiology Study done in India (67). A study conducted in older subjects in Pakistan (aged 40 years and above) showed a prevalence rate of 45.9% in males and 57.2% in females (117).

Differences by gender in subjects with metabolic syndrome are also evident from different ethnic-based studies (48,67,118). The high prevalence of low HDL-C and obesity, as seen in our women, has also been reported among Indian women and other South Asian women (67,119,120). This may indicate similar lifestyle factors, such as food habits and less physical activity, which may have influenced the outcome in women of Indian subcontinent.

The prevalence of metabolic syndrome increased with advancing age in both genders using ATP III and IDF definitions, a trend seen in other studies done in South Asian and U.S. populations (56,57,65,68). The study also shows that there is greater prevalence of hypertension, obesity and low HDL in subjects with metabolic syndrome. Thus leading to the

conclusion that the contributing causes of this syndrome are similar everywhere. There appears to be a very high prevalence of low HDL cholesterol in men and women in our metabolic syndrome group (≥ 85%). A similarly high prevalence of low HDL cholesterol in women was also seen in Indian studies (63).

The present study results are not comparable with any previous Pakistani study as metabolic syndrome is a new entity and the modified IDF definition has only recently been introduced. Thus we observed a high rate of metabolic syndrome in the urban population of Lyari Town in the city of Karachi.

4.8.4 Dietary Trends in South Asians leading to Metabolic Syndrome

The interaction between different components of diet as well as the consumption of different food items contributes to the risk for metabolic syndrome and not one single dietary component which is responsible for the association of diet with metabolic syndrome. Thus overall dietary trends need to be observed in individuals as they consume a mixture of different food items in a single meal, rather than isolated groups.

In the dietary section of our study low MS risk group (cluster 1) had lowest consumption of all the food groups while the high MS risk group (cluster 2) had the highest consumption in most of the food groups. This high food consumption seems to contribute to the high prevalence of MS as seen in cluster 2. Looking at the food groups individually it appears that the food items which were the most energy-dense had the highest consumption in cluster 2, and probably influencing in creating an unhealthy dietary pattern which leads to increased prevalence of MS.

It has been observed in other studies that the consumption of traditional food (low in saturated fat, low in simple sugars and high in fibre) has declined recently and energy-dense food (high in calories, carbohydrates and saturated fats and low in fibre) and non-traditional energy-dense fast food are being increasingly consumed in South Asia (59,75).

Studies have also shown that South Asians have a high consumption of dairy products and sugar compared to other populations (75,124). Although dairy consumption has been inversely related to MS in some studies (125-127) more than twice dairy consumption was seen in the high risk group. Looking further at the individual food items in the milk group it was observed that the highest consumption was in cream\custard and ice cream\sweet lassi; items which have a high fat and sugar content. Coincidently a high intake of fat, milk products and sugars in various regions of India have shown to be associated with increased cardiovascular mortality (128). Thus a combination of dairy products, with high fat and sugars may influence the individual properties of food and produce a positive association

with metabolic syndrome. In our study these factors probably made dairy consumption lose its protective effect in our subjects as documented elsewhere (127).

Red meat, organ meat and prawns from the meat group were consumed 3 to 5 times more in cluster 2 compared to cluster 1. All of these food items are known to be high in saturated fat, which has been adversely associated with cholesterol, blood pressure, obesity and diabetes risk (129-131).

Similarly all the food items in fat & sweet group were consumed five times more in cluster 2 compared to cluster 1. Sweet products were consumed an alarming 13 times more in cluster 2 and they probably influenced the increased prevalence of MS in cluster 2 with their load of empty calories in the diet.

South Asians consume more carbohydrates compared to Europeans and this may lead to hyperinsulinemia, postprandial hyperglycaemia, hypertriglyceridemia and low HDL cholesterol levels, all of which is probably due to insulin resistance (87). Processed cereals, such as refined grains have been shown to be associated with an increased risk of the components of the metabolic syndrome in The Malmö Diet and Cancer Study (132). In our study refined grains were also consumed nearly twice in the high MS risk group (cluster 2).

Although nearly double consumption of raw vegetables was seen in cluster 2 compared to cluster 1 and while double consumption of the fruit group was also seen in cluster 2, looking at the individual food items in the fruit group it seems that the consumption of fruit juices was 8 times more in cluster 2 compared to cluster 1 which would lead to extra empty calories. Despite the fact that an inverse association between prevalent MS and intakes of fruit and vegetables has been reported previously, the extra empty calories leads to increased prevalence of MS undermining the protective effect of vegetables and fruits on cluster 2 (130,133-134).

4.8.5 Defining Insulin Resistance

Insulin Resistance (IR) is an acronym for a wide range of metabolic derangements with convincing evidence that it is an independent risk factor for a number of chronic diseases such as diabetes and cardiovascular diseases (CVD). Insulin resistance has also been suggested as the primary cause leading to the clustering of risk factors such as glucose intolerance, hypertension, elevated serum triglycerides, low serum HDL cholesterol and central obesity which together have been labeled as the Metabolic syndrome (MS) (37). Thus diagnosis of insulin resistance at the initial stages of a disease could be used as a effective measure to prevent unfavourable outcome.

Researchers have suggested that a fasting insulin level at 75^{th} percentile cutoff is accurate at predicting insulin resistance in normal non diabetic population in some studies (135,136).

Fasting insulin levels at 75th percentile was also used as a cut off value in this study and this value lies within the range observed in other studies (135,142,143).

Insulin resistance indices have been developed based on fasting blood samples (serum insulin and glucose levels) which can be used as reference cutoffs defined for various populations (135). The homeostasis model for insulin resistance (HOMA-IR), the quantitative insulin sensitivity check index (QUICKI) and McAuley Index are commonly used surrogate measures from these fasting values and have proven to be a reliable alternative to the glucose clamp studies (136-138). Many studies using these simple indirect methods for detecting insulin resistance have been reported (139-141).

4.8.5.1 Insulin resistance indices

In 1985 Matthews was one of the pioneers to define homeostasis model for insulin resistance (HOMA-IR) as a simple and reliable method for estimating insulin sensitivity from fasting plasma glucose and insulin levels (138). The non-linearity of the model precludes an exact algebraic solution, but estimations are possible by using mathematical approximations:

HOMA-B = Insulin (mU/ml) × 20/ glucose (mmol/l) - 3.5

HOMA-R = Insulin (mU/ml) × glucose (mmol/l)/22.5

Low HOMA values indicate high insulin sensitivity, whereas high HOMA values indicate low insulin sensitivity.

HOMA-IR values between 1.21 and 1.45 were reported for normal subjects by Matthews (138). Many large population-based studies have used HOMA-IR to assess insulin sensitivity and reported HOMA-IR to be around 2.6 on the basis of the 75th percentile (137, 140-142). However lower HOMA-IR values have been observed in south asians with an Indian study reporting HOMA-IR to be 1.93 at the 75th percentile while in our study it was observed to be even lower at 1.82 (144).

Taking 75th percentile of HOMA-IR as a cut-off for insulin resistance we compared insulin resistance group (HOMA-IR > 1.82) with non insulin resistance group (HOMA-IR < 1.82) and observed that age, hypertension (systolic and diastolic blood pressure), being overweight (as assessed by waist circumference or Body Mass Index), triglycerides and urinary micro-albuminuria were increased in insulin resistant group compared to normal group while HDL was decreased in the insulin resistant group. A large number of other epidemiological and clinical studies have firmly established consistent correlations between anthropometric, metabolic and homodynamic variables of insulin resistance. These variables include obesity, unfavourable body fat distribution, glucose intolerance or type2 diabetes, hyperinsulinemia,

low levels of HDL hypertriglyceridemia, high levels of LDL and hypertension; some of which were also seen in our study.

Other researchers suggested QUICKI to be a better surrogate measure of insulin resistance than HOMA-IR (139). The 25th percentile value of QUICKI was 0.347 in our study which lies within the range reported for normal populations (0.33-0.372) by other researchers (142).

It has been suggested by some researchers that incorporating triglycerides in asian subjects increases the likelihood of identifying insulin resistance (144). The index proposed by McAuley for the diagnosis of insulin resistance does this by incorporating triglycerides in its formula (135). We calculated McAuley index on the basis of the 25th percentile and in our study the cutoff of McAuley index was 6.77.

Although determining insulin resistance by indirect methods is difficult due to the variability of results, but the cut off values of IR determined can be used as a measure of insulin resistance in Pakistani adults. It is hoped that a common approach towards managing subjects with metabolic risk factors by using a single cutoff value will help save time and improve clinical assessment by identifying such cases of insulin resistance earlier. Secondly the clinical focus may shift from identifying the various risk factors separately towards identifying insulin resistance by using reference values measured from these simple indirect methods.

4.8.6 Primary Prevention Study

Our results suggest that lifestyle intervention is highly effective in preventing high risk individuals (IGT) from conversion to diabetes in this population. Adding oral hypoglycaemic agent (metformin) in addition to lifestyle modification was not found to be advantageous for prevention. These results are in line with previous studies done in other populations (145-149).

The progression rate of IGT to diabetes in our control group was lower compared to Indian and Chinese controls (8.2% per 12 months compared to 18.3% and 11.3% per 12 months respectively) (145,146). But it was still significantly higher than seen in the Finnish (6% per year) and DPP (11 per 100 person-years) studies (147-149). All subjects in the control group also received general health advice about diet, nutrition and exercise at baseline and at subsequent follow-up visits. This might have increased their diabetes risk awareness and some subjects may have benefited from this advice. A absolute reduction of 10.7/100 was seen in the intensive lifestyle group, which was greater than seen in IDPP (15.7/100) (145). More number of subjects were needed to treat in order to prevent one case of diabetes in the intensive group in our study (9 vs 6.4) compared to IDPP (145).

The baseline characteristics appear to be similar in our subjects compared to other Asian studies (Mean age Indian 45.9±5.7 years, Chinese 45±9.1 years vs. our mean age 43.6±9.9 years) but had comparatively higher BMI (kg/m2) (Indian 25.8±3.5 kg/m2, Chinese 25.8±3.8 kg/m2 and ours 27.1±5.0 kg/m2) (145,146). Our subjects were younger and leaner compared to the Finnish (age 55±7.0 years, BMI 31±4.6 kg/m2) and the American subjects (age 50.6±10.7 years, BMI 34±6.7 kg/m2) (6;8). The follow-up period in our study was half in duration (only 18 months) compared to the Indian, American and Finnish studies (145-149). In our study the progression of IGT to diabetes was comparable to other Asian studies and showed the effectiveness of lifestyle modification involving moderate physical activity and diet modification to prevent diabetes in this population. Adding metformin had a slight additional benefit but its impact was quite small with relative risk reduction decreasing by 5.5%, from 71% to 76.5% in the lifestyle modification+drug group. This difference was not found to be statistically significant.

Our findings showed that in order to reduce the burden of diabetes epidemic, effective primary prevention can be achieved through lifestyle modification. Therefore, it is suggested that necessary policy development on the prevention of diabetes should emphasize on lifestyle modification. The main motivation for the prevention of type 2 diabetes is that it can prevent or delay the onset of diabetes and its complications, thereby reducing the life entrenched financial burden and unnecessary human sufferings of diabetes on both the individual and on the society at large. Developing countries have to face this additional burden on their already ailing economy (150,151); therefore, primary prevention programmes need to become a integral part of Primary Health Services and strategies for reducing the diabetes burden at all levels.

5 Implications of the results

The prevalence of the metabolic syndrome was found to be between 12% - 49% using the various definitions of metabolic syndrome. We focused on the modified ATP III and IDF definitions as they provide an accessible diagnostic tool which is suitable for use and establish a list of potential additional criteria that could be included in epidemiological studies and other research into the metabolic syndrome.

The prevalence of metabolic syndrome increases with advancing age for both males and females The study showed greater prevalence of hypertension, obesity and low HDL in subjects with metabolic syndrome.

More than half of our study population does not do any sort of physical exercise and lead a sedentary lifestyle. Similar contributing factors of this syndrome have been observed elsewhere with obesity and sedentary lifestyle in the forerun. Bearing this in mind we designed a diabetes prevention program to be implemented in our local population.
In several randomized trials, drug therapy has proven effective in the prevention of type 2 diabetes. However, drug intervention has been shown to be less effective than therapeutic lifestyle interventions. Our study shows the efficacy of lifestyle modifications as a means of primary prevention in a population having distinctive environmental conditions and genetic propensity as was seen in the Indian Diabetes Prevention Programme for the Indian population.

Our studies have helped to compile population based data, monitor disease trends, and create an environment that will be conducive to promoting healthy lifestyles through multi-sectorial, inter-disciplinary collaborations.

Recent Updates from the China DaQing Prevention Study, the Finnish Diabetes Prevention Study, the American Diabetes Prevention Programme Outcome Study and the Look Ahead Study have all shown that the most efficient way to manage diabetes and its complications is to prevent diabetes in the first place. This in turn has lead to policy documents from expert organizations such as The Disease Control Priorities project (DCP-2), the European Society of Cardiology and European Association for the Study of Diabetes, the Canadian Diabetes Association, the American Diabetes Association, and the International Diabetes

Federation, all recommending lifestyle changes such as weight loss and increased physical activity for the prevention of T2DM among those with pre-diabetes (82,145,152-156).

Policy changes and community mobilization schemes need to be initiated. Lifestyle modification programmes with particular emphasis on increasing physical activity (30 minutes of brisk walking), adhering to a balanced diet (high in fibre and low in fat), and losing 5% body weight which has shown to reduce the risk of progression from impaired glucose tolerance to diabetes need to be initiated.

6 Conclusion

Based on the findings of the epidemiological survey we implemented the primary prevention trial since the metabolic syndrome should be considered as a prime target for preventive medicine; and as the emerging global epidemic of metabolic and vascular disease has significant implications for the development of population based health policies.

Despite the challenges involved in day-to-day life, the non-pharmacological lifestyle modification approach to prevention of the metabolic syndrome is shown to be effective in our study. A large number of lifestyle-related risk factors are associated with the metabolic syndrome and diabetes as seen in the lyari survey. Therefore we need to increase people's awareness about these risk factors by seminars and public events and to highlight the significant of a healthy lifestyle.

IDF and WHO have made recommendations for the development of nationwide surveillance and prevention programmes against non-communicable diseases, including diabetes. The results from our study can be used as a pilot project for launching such programs within the communities making them relevant to our cultural needs, and help the government and advocacy groups within the country to translate this evidence into culturally accepted clinical practice to initiate a national diabetes prevention and control program.

In order to reduce the diabetes burden and stop treating the majority of the cases when they reached the steeper extreme of the road a nationwide community based diabetes primary prevention program needs to be started. This is important, particularly at a time when the global epidemic of metabolic and vascular disease is emerging as a significant public health challenge, with its consequences for diabetes and CVD.

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8 Appendix I(Questionnaire of First Study)

Informed Consent

Diabetic Association of Pakistan and World Health Organization Collaborating Center

CONSENT FORM

Title of Research Project:

Prevalence of Type 2 Diabetes and Associated Risk Factors among Adults 25 Years and Above in Urban Karachi

Explanation of Research Project:

PURPOSE OF STUDY

The doctors and health workers here are working with researchers at

- Diabetic Association of Pakistan and World Health Organization Collaborating Centre;
- Interactive Communications Research and Development Division;
- Baqai Institute of Diabetology and Endocrinology
- Lyari Community Development Project

to find out about diabetes and heart disease in adults. Your household has been selected randomly from a list of all households in Lyari / North Nazimabad. The researchers undertaking this survey would like to ask you to participate in this study.

PROCEDURES

If you agree we will ask you questions about

- your household and members of your household.
- your lifestyle (e.g. diet, exercise) and existing conditions related to diabetes and heart disease.

We will take measurements of your height, weight, hips, waist, abdomen and blood pressure. The doctors would like to take a blood sample from you after you have fasted overnight to test for high levels of glucose, lipids and liver enzymes. You will be informed of the glucose test results within 3 days but the results of some of the other tests will take longer.

Do you agree to provide blood to test for glucose, lipids and liver enzymes: Yes __; No ___

We would also like to store your blood sample to test for infections that might cause liver disease. The blood sample may be stored for up to 10 years. The samples will be stored in a manner that will not identify you by name. The results from these future tests may not be available to you.

Do you agree to let the blood sample be stored for up to 10 years for future research?
Yes ____; No _____

The data from the study will be kept in an office in Karachi. Information about your child will be available only to people working on the study. We will keep the study information private to the extent possible by the laws of Pakistan. People responsible for making sure that the research is done properly may review your study records. This might include people from the Baqai Institute of Diabetology and Endocrinology and the Lyari Community Development Project.

RISKS AND DISCOMFORTS

If blood is taken the needle stick may cause some discomfort and bruising.

BENEFITS

The test results will be given to you. Any doctors that you visit will benefit by finding out if you have diabetes or risk factors for diabetes and heart disease. This information will also help researchers and doctors in understanding the causes of diabetes and heart disease in adults in Lyari / North Nazimabad and to plan programs to prevent these diseases. If you do not have diabetes or risk factors for diabetes and heart disease, you will be able to continue your lifestyle knowing that you are at low risk. You will not receive any payment for participating in this study.

You are not forced to be in this study. You may leave the study at any time. If you decide not to be in the study, your care or relations with your doctors will not be changed in any way. You should ask the project coordinator any questions you may have about this study. You may ask him/her questions in the future if you do not understand anything. The researchers will tell you any new information that they may find out while you are in this study.

If you think being in the study has hurt you, you have not been treated fairly you can call the Principal Investigator Dr. A Samad Shera at 661-6890 (Karachi). You can also call the Project Coordinator Dr. Aamir Khan at 439-6254 (Karachi). You can also call Dr. Abdul Basit at the Baqai Institute of Diabetology and Endocrinology at 661-7234 (Karachi) and Mr. Abdur Rahim Moosvi at the Lyari Community Development Project at 752-1687 (Karachi).

If you agree to participate in this study please sing your name below.

Void One Year From Above Date
No. _____
Approved From _____ to _____

_____
Signature

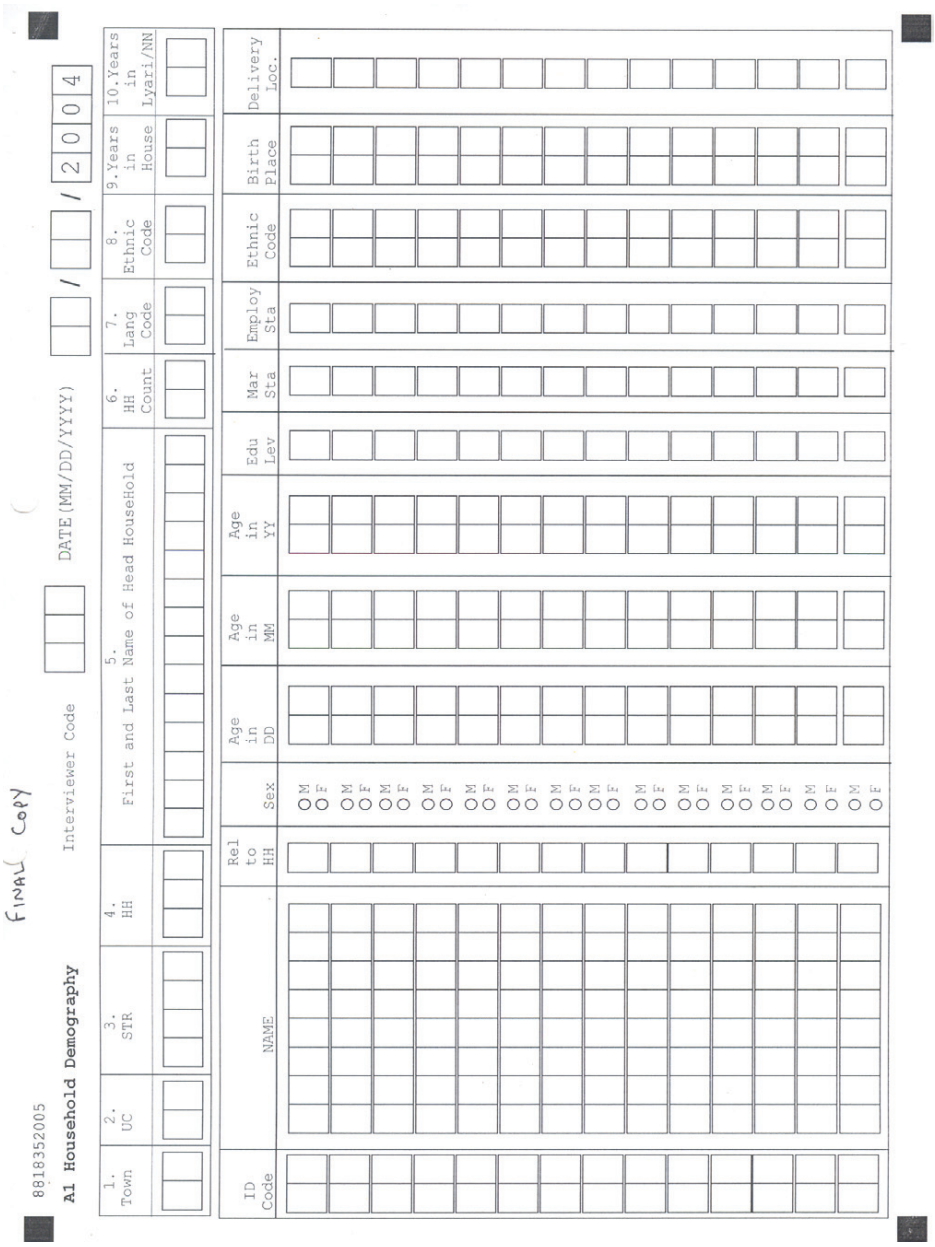
_____
*Witness to Consent Procedures**

_____
Signature of Investigator

_____
Date
**Optional unless subject is illiterate, or unable to sign*

Note: *Signed copies of this form must be a) retained in file by the Principal Investigator, b) given to the participant and c) put in the patient's medical record (when applicable).*

Structured Interview Questionnaire (11 Pages)



6705376734 IC House UID

A2 House Hold Diet

A2.1 What kinds of fat do you usually use in cooking (e.g. cooking salan, frying etc.)?

- ☐ Banaspati Ghee
- ☐ Asli Ghee
- ☐ Oil
- ☐ Butter
- ☐ Margarine

Others

A2.2 What brand of Ghee/Oil do you use?

Ghee

Oil

A2.3 How much banaspati ghee do you use per day or per week?

No	Frequency	KG	GM
1	Daily		
2	Weekly		
3	Monthly		

A2.4 How much Asli ghee do you use per day or per week

No	Frequency	KG	GM
1	Daily		
2	Weekly		
3	Monthly		

A2.5 How much oil do you use per day or per week?

No	Frequency	KG	GM
1	Daily		
2	Weekly		
3	Monthly		

A2.6 On an average how much salt do you buy (packets) in one month? Pack gm/pack

A2.7 Do you usually use same food dishes in lunch and dinner? ○ Y ○ N

A2.8 For how many people, above age 1, is food cooked at home daily?

7991431464 IC House UID

A3 Socioeconomic Status

A3.1	Main Type of construction of house 1.Pucca 2.Semi-pucca Roof Walls Floor 3.Katcha	R W F
A3.1a	What is the house type/size 1.Hut 2.House(<80 sq.yards) 3.Town House (80-240 sq.yards) 4.Bunglow (300-500 sq.yards) 5.Bunglow (500+ ssq.yards) 6.Ordinary Flat(2 rooms or les) 7.Luxury Flat(3 or more rooms)	
A3.2	Do you own this house 1.Yes,Own, 2.No,on rent 3.No,office accommodation 4.No,relative house	
A3.2a	What is the monthly rent or expected rent, if owned?	Amount in Rs 99999. Dont know
A3.3	How many rooms are altogether in this house(excluding Kitchen,bath/toilet, store,veranda)?	write actual number of rooms *if more than one households in one structure,ask how many of these are used by this household
A3.4	What is the main source of water this house hold uses for bathing and washing. 4.Community Tap; 5.Community Hand Pump ;6.Community well/boring 7.Tanker; 8.Other.please specify; 9.Water Bought	1.Tap inside 2.Hand Pump Inside 3.Well/boring inside if others pls specify Others
A3.4.1	Does this household get drinking water from the same source? 3.No,other tap; 4.No, other hand pump; 5.No,other well/boring; 6.other..please specify	1.Yes,same source 2.No,bottled water if others pls specify Others
A3.5	What type of toilet facility does this house have? 5.Public Latrine; 6.Other plese specify	1.Use open Space 2.Bucket 3.Flush latrine 4.Close pit if others pls specify Others
A3.6	Does this house have a seprate Kitchen 1.Yes,seprate 2.No, in a living room; 3.No,in an open verandah; 4.No,in an open space	
A3.7	Does this house have electricity	○ Y ○ N
A3.8	Does this house have a sui gas connection	○ Y ○ N

A3.9	Does this household have/own any of the following.	
A3.9a	Refrigerator	○ Y ○ N
A3.9b	TV (Color)	○ Y ○ N
A3.9c	TV (Black & White)	○ Y ○ N
A3.9d	Dish Antenna/Cable	○ Y ○ N
A3.9e	Washing machine	○ Y ○ N
A3.9f	Telephone	○ Y ○ N
A3.9g	Computer	○ Y ○ N
A3.9h	Scooter/Motor cycle	○ Y ○ N
A3.9i	Car/Suzuki/jeep/van	○ Y ○ N

Income Range

A3.10	Kindly provide information on all kinds of income to this household.	
A3.10a	During Last MONTH	
A3.10b	During Last YEAR	

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B1 Personal Medical History

اس حصّہ میں، میں آپ سے آپ کی صحت کے متعلق پوچھوں گا/ گی۔

B1.1	**ہائی بلڈ پریشر** کیا آپ سے کبھی کسی نے کہا ہے کہ آپ کو ہائی بلڈ پریشر ہے؟ اگر نہیں تو، سوال نمبر B1.5 پر جائیں۔	○ Y ○ N
B1.2	کیا آپ کو کبھی معالج نے بتایا ہے کہ آپ کو ہائی بلڈ پریشر کی بیماری ہے؟ اگر نہیں تو، سوال نمبر B1.5 پر جائیں۔	○ Y ○ N
B1.3	اس وقت آپ کی عمر کیا تھی جب آپ کو بتایا گیا کہ آپ کو ہائی بلڈ پریشر ہے؟	☐☐
B1.4	ہائی بلڈ پریشر کی وجہ سے آپ کے معالج نے کبھی آپ کو تجویز کردہ دوائی استعمال کرنے کے لئے کہا؟	○ Y ○ N
B1.5	**دل کی بیماری** کیا آپ کو کبھی کسی معالج نے بتایا ہے کہ آپ کو دل کی بیماری ہے؟ اگر نہیں تو، سوال نمبر B1.10 پر جائیں۔	○ Y ○ N ○ DK
B1.6	وہ دل کی بیماری کیا تھی؟	○ Heart Attack ○ Angina Others ☐☐ ☐☐☐☐☐☐☐☐
B1.7	جب آپ کو بتایا گیا کہ آپ کو دل کی بیماری ہے تو اس وقت آپ کی عمر کیا تھی؟	☐☐
B1.8	کیا اس کیلئے آپ کو کوئی دوا تجویز کی گئی؟	○ Y ○ N
B1.9	اگر ہاں، تو علاج کی نوعیت کیا تھی؟	○ سرجیکل ○ سرجیکل اور غیر سرجیکل
B1.10	**گردوں کی بیماری** کیا آپ کو کبھی معالج نے بتایا ہے کہ آپ کو گردوں کی بیماری ہے؟ اگر نہیں تو، سوال نمبر B1.14 پر جائیں۔	○ Y ○ N ○ DK
B1.11	جب آپ کو بتایا گیا کہ آپ کو گردوں کی بیماری ہے تو اس وقت آپ کی عمر کیا تھی؟	☐☐
B1.12	کیا اس کیلئے آپ کو کوئی دوا تجویز کی گئی؟ اگر نہیں تو، سوال نمبر B1.14 پر جائیں۔	○ Y ○ N
B1.13	اگر ہاں، تو علاج کی نوعیت کیا تھی؟	○ سرجیکل ○ سرجیکل اور غیر سرجیکل
B1.14	**ذیابیطس** کیا آپ کو کبھی کسی معالج نے بتایا ہے کہ آپ کو شوگر کی بیماری ہے اگر نہیں تو، سوال نمبر B1.19 پر جائیں۔	○ Y ○ N ○ DK ○ Had Symptoms ○ Screening only
B1.15	آپ کو کیسے تشخیص ہوا کہ آپ کو شوگر کی بیماری ہے؟	Others ☐☐ ☐☐☐☐☐☐☐☐
B1.16	جب آپ کو بتایا گیا کہ آپ کو شوگر کی بیماری ہے تو اس وقت آپ کی عمر کیا تھی؟	☐☐
B1.17	کیا اس کیلئے آپ کو کوئی دوا تجویز کی گئی؟	○ Y ○ N
B1.18	اگر ہاں، تو کون سی دوا؟	☐ Insulin ☐ Tablets ☐ Diet only Others ☐☐ ☐☐☐☐☐☐☐☐
B1.19	**فالج** کیا آپ کو کبھی فالج کا اٹیک / حملہ ہوا ہے؟ اگر نہیں تو، سوال نمبر B1.22 اگر نہیں تو، پر جائیں۔	○ Y ○ N
B1.20	جب آپ کو بتایا گیا کہ آپ کو فالج کا حملہ ہوا ہے تو اس وقت آپ کی عمر کیا تھی؟	☐☐
B1.21	کیا اس کیلئے آپ کو کوئی دوا تجویز کی گئی؟	○ Y ○ N
B1.22	کیا آپ آجکل کوئی دوائی استعمال کر رہے ہیں؟	○ Y ○ N
B1.23	آپ کس بیماری کے لیے دوا لے رہے ہیں؟	☐ BP ☐ Cholestrol ☐ CVD ☐ Other ☐ Diabetics
B1.24	کیا آپ کو کسی معالج نے بتایا کے آپ کو دمہ یا پھیپھڑوں کی بیماری ہے؟ اگر ہاں تو کون سی؟	○ Y ○ N ☐ دمہ ☐ پھیپھڑوں کی بیماری

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B2 Family Medical History

B2.1	اپ کی عمر کیا ہے؟	☐☐
B2.2	اگر اپ شادی شدہ ہے، تو کیا اپ کی بیوی/شوہر اپ کے (First Cousin) ہے؟	○ Y ○ N ○ NA
	ہائی بلڈ پریشر	
B2.3	کیا آپ کے قریبی خاندان کے کسی بھی فرد کو کبھی معالج نے بتایا ہے کہ اسے ہائی بلڈ پریشر کی بیماری ہے؟ *(If No or Don't know, skip to B2.5)*	○ Y ○ N ○ DK
B2.4	اگر ہاں تو کس کو؟	☐ والدین ☐ بہائی/بہن ☐ ( )
	دل کی بیماری	
B2.5	کیا آپ کے قریبی خاندان کے کسی بھی فرد کو کبھی معالج نے بتایا ہے کہ اُسے دل کی تکلیف یا ہارٹ اٹیک ہوا ہے؟ *(If "No" or "Don't Know" skip to B2.7)*	○ Y ○ N ○ DK
B2.6	اگر ہاں تو کس کو؟	☐ والدین ☐ بہائی/بہن ☐ ( )
	ذیابیطس	
B2.7	کیا آپ کے قریبی خاندان کے کسی بھی فرد کو کبھی معالج نے بتایا ہے کہ اُسے شوگر کی بیماری ہے؟ *(If "No" or "Don't Know" skip to B2.9)*	○ Y ○ N ○ DK
B2.8	اگر ہاں تو کس کو؟	☐ والدین ☐ بہائی/بہن ☐ ( )
	فالج	
B2.9	کیا آپ کے قریبی خاندان کے کسی بھی فرد کو کبھی معالج نے بتایا ہے کہ اُسے فالج کا حملہ ہوا ہے؟ *(If "No" or "Don't Know" skip to B2.11)*	○ Y ○ N ○ DK
B2.10	اگر ہاں تو کس کو؟	☐ والدین ☐ بہائی/بہن ☐ ( )
B2.11	کیا آپ کی والدہ ابھی حیات ہیں؟	○ Y ○ N
	اگر ہاں تو سوال نمبر B2.14 پر جائیں	
B2.12	جب آپ کی والدہ کا انتقال ہوا تب ان کی عمر کیا تھی؟	☐☐
B2.13	ان کے انتقال کی وجہ کیا تھی؟	☐ دل کا دورہ ☐ فالج ☐ کینسر ☐ ذیابیطس ☐ پتہ نہیں Others ☐☐ ☐☐☐☐☐☐☐☐☐☐
B2.14	کیا آپ کی والد ابھی حیات ہیں؟	○ Y ○ N
	اگر ہاں تو سوال نمبر B3 پر جائیں	
B2.15	جب آپ کے والد کا انتقال ہوا تب ان کی عمر کیا تھی؟	☐☐
B2.16	ان کے انتقال کی وجہ کیا تھی؟	☐ دل کا دورہ ☐ فالج ☐ کینسر ☐ ذیابیطس ☐ پتہ نہیں Others ☐☐ ☐☐☐☐☐☐☐☐☐☐

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B3 Tobacco Use

	سگریٹ / سگار / بیڑی	
B3.1	کیا آپ نے اپنی زندگی میں کبھی سگریٹ / سگار / بیڑی پی ہے؟ (اگر نہیں تو سوال نمبر B3.9 پر جائیں)	○ Y ○ N
B3.2	آپ نے کس عمر میں سگریٹ / سگار / بیڑی پینا شروع کی؟	[ ][ ]
B3.3	کیا آپ آج کل سگریٹ / سگار / بیڑی پیتے ہیں؟ (اگر نہیں تو سوال نمبر B3.6 پر جائیں)	○ Y ○ N
B3.4	اوسطاً آپ دن میں کتنی سگریٹ / سگار / بیڑی پیتے ہیں؟	[ ][ ]
B3.5	کیا یہ سگریٹ / سگار / بیڑی فلٹر والے یا بغیر فلٹر والے ہوتے ہیں؟ (اب آپ سوال نمبر B3.9 پر جائیں)	○ Filter ○ Non Filter
B3.6	اوسطاً آپ ایک دن میں کتنی سگریٹ / سگار / بیڑی پیا کرتے تھے؟	[ ][ ]
B3.7	آپ نے کس عمر میں سگریٹ / سگار / بیڑی پینا چھوڑ دی؟	[ ][ ]
B3.8	آپ نے سگریٹ / سگار / بیڑی پینا کیوں چھوڑ دی؟	[ ][ ][ ][ ][ ][ ][ ][ ]
	حقہ / پائپ	
B3.9	کیا آپ نے اپنی زندگی میں کبھی حقہ / پائپ پیا ہے؟ (اگر نہیں تو سوال نمبر B3.16 پر جائیں)	○ Y ○ N
B3.10	آپ نے کس عمر میں حقہ / پائپ پینا شروع کیا؟	[ ][ ]
B3.11	کیا آپ آج کل حقہ / پائپ پیتے ہیں؟ (اگر نہیں تو سوال نمبر B3.13 پر جائیں)	○ Y ○ N
B3.12	اوسطاً آپ ایک ہفتے میں کتنا تمباکو استعمال کرتے ہیں؟ (اب آپ سوال نمبر B3.16 پر جائیں)	[ ][ ][ ][ ] gms
B3.13	اوسطاً آپ ایک ہفتے میں کتنا تمباکو استعمال کرتے تھے؟	[ ][ ][ ][ ] gms
B3.14	آپ نے کس عمر میں حقہ / پائپ پینا چھوڑا؟	[ ][ ]
B3.15	آپ نے حقہ / پائپ پینا کیوں چھوڑا؟	[ ][ ][ ][ ][ ][ ][ ][ ]
	نسوار	
B3.16	کیا آپ نے اپنی زندگی میں کبھی نسوار استعمال کی ہے؟ (اگر نہیں تو سوال نمبر B3.23 پر جائیں)	○ Y ○ N
B3.17	آپ نے کس عمر میں نسوار استعمال کرنا شروع کی؟	[ ][ ]
B3.18	کیا آپ آج کل نسوار استعمال کرتے ہیں؟ (اگر نہیں تو سوال نمبر B3.20 پر جائیں)	○ Y ○ N
B3.19	اوسطاً آپ ایک دن میں کتنی مرتبہ نسوار استعمال کرتے ہیں؟ (اب آپ سوال نمبر B3.23 پر جائیں)	[ ][ ]
B3.20	اوسطاً آپ ایک دن میں کتنی نسوار استعمال کرتے تھے؟	[ ][ ][ ][ ][ ] gms
B3.21	آپ نے کس عمر میں نسوار کا استعمال چھوڑا؟	[ ][ ]
B3.22	آپ نے نسوار کا استعمال کیوں چھوڑا؟	[ ][ ][ ][ ][ ][ ][ ][ ]
	پان یا بغیر پان تمباکو چبانا	
B3.23	کیا آپ نے اپنی زندگی میں کبھی پان یا بغیر پان تمباکو چبایا ہے؟ (اگر نہیں تو سوال نمبر B4.1 پر جائیں)	○ Y ○ N
B3.24	آپ نے کس عمر میں پان یا بغیر پان تمباکو چبانا شروع کیا؟	[ ][ ]
B3.25	کیا آپ آج کل پان یا بغیر پان تمباکو چباتے ہیں؟ (اگر نہیں تو سوال نمبر B3.27 پر جائیں)	○ Y ○ N
B3.26	اوسطاً آپ ایک دن میں پان یا بغیر پان تمباکو چباتے ہیں؟ (اب آپ سوال نمبر B4.1 پر جائیں)	[ ][ ]
B3.27	اوسطاً آپ ایک دن میں پان یا بغیر پان تمباکو چباتے تھے؟	[ ][ ][ ][ ] gms
B3.28	آپ نے کس عمر میں پان یا بغیر پان تمباکو چبانا چھوڑا؟	[ ][ ]
B3.29	آپ نے پان یا بغیر پان تمباکو چبانا کیوں چھوڑا؟	[ ][ ][ ][ ][ ][ ][ ][ ]

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B4 Personal Diet

اب میں آپ سے مختلف کھانوں کے بارے میں پوچھوں گا/ گی، اور میں چاہوں گا/ گی کہ آپ مجھے ایک بار بتائیں کہ کتنی مرتبہ یہ کھانے ایک دن میں، ہفتے میں یا مہینے میں کھاتے ہیں یا پھر کبھی کبھار/ کبھی نہیں کھاتے۔

No.	FOOD Items	کبھی نہیں	مہینہ /	ہفتہ /	دن /
B4.1	انڈا	☐	☐☐	☐☐	☐☐
B4.2	پراٹھا	☐	☐☐	☐☐	☐☐
B4.3	تندوری نان	☐	☐☐	☐☐	☐☐
B4.4	حلوہ پوری	☐	☐☐	☐☐	☐☐
B4.5	دودھ بالائی کے ساتھ	☐	☐☐	☐☐	☐☐
B4.6	دودھ بغیر بالائی کے ساتھ	☐	☐☐	☐☐	☐☐
B4.7	بالائی یا ملائی	☐	☐☐	☐☐	☐☐
B4.8	میٹھا مثلاً کسٹرڈ، کھیر، فرنی وغیرہ	☐	☐☐	☐☐	☐☐
B4.9	آئس کریم	☐	☐☐	☐☐	☐☐
B4.10	دہی	☐	☐☐	☐☐	☐☐
B4.11	میٹھی لسی	☐	☐☐	☐☐	☐☐
B4.12	نمکین لسی	☐	☐☐	☐☐	☐☐
B4.13	مارجرین	☐	☐☐	☐☐	☐☐
B4.14	مکھن	☐	☐☐	☐☐	☐☐
B4.15	بکرے کا گوشت (سالن، روسٹ وغیرہ)	☐	☐☐	☐☐	☐☐
B4.16	گائے کا گوشت (سالن، روسٹ، کباب، قیمہ وغیرہ)	☐	☐☐	☐☐	☐☐
B4.17	مرغی (سالن، روسٹ، تکہ وغیرہ)	☐	☐☐	☐☐	☐☐
B4.18	مچھلی (سالن، فرائی وغیرہ)	☐	☐☐	☐☐	☐☐
B4.19	جھینگے	☐	☐☐	☐☐	☐☐
B4.20	مغز، کلیجی، گردے وغیرہ	☐	☐☐	☐☐	☐☐
B4.21	باہر سے خریدے ہوئے کھانے مثلاً کٹلٹ، کڑاہی، نہاری، برگر، پیزا وغیرہ	☐	☐☐	☐☐	☐☐
B4.22	پکی ہوئی سبزیاں (آلو شامل نہیں)	☐	☐☐	☐☐	☐☐
B4.23	آلو (بتھول دوسری سبزیوں اور گوشت)	☐	☐☐	☐☐	☐☐
B4.24	کچی سبزیاں (سلاد وغیرہ)	☐	☐☐	☐☐	☐☐
B4.25	بریانی، پلاؤ	☐	☐☐	☐☐	☐☐
B4.26	دالیں، لوبیا، مٹر وغیرہ	☐	☐☐	☐☐	☐☐
B4.27	پھل (جوس شامل نہیں)	☐	☐☐	☐☐	☐☐
B4.28	تازہ پھلوں کے جوس (پیکٹ کے جوس شامل نہیں)	☐	☐☐	☐☐	☐☐
B4.29	بیکری کی اشیاء (کیک، پیسٹری، بسکٹ وغیرہ)	☐	☐☐	☐☐	☐☐
B4.30	مٹھائی، حلوہ	☐	☐☐	☐☐	☐☐
B4.31	نمکین اور تلی ہوئی اشیاء مثلاً آلو چپس، پکوڑے، سموسہ، نمکو، پاپ کارن وغیرہ	☐	☐☐	☐☐	☐☐
B4.32	مونگ پھلی، بادام، چلغوزہ، اخروٹ وغیرہ	☐	☐☐	☐☐	☐☐
B4.33	چاکلیٹ و دیگر ٹافیاں	☐	☐☐	☐☐	☐☐
B4.34	کوئی اور ایسی اشیاء جو آپ استعمال کرتے ہو اور ہم نے نہ پوچھی ہو۔	☐	☐☐	☐☐	☐☐

Countined.....

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B6 Physical Activity

ہم ان جسمانی کاموں کے بارے میں جاننا چاہتے ہیں جو لوگ روزمرہ زندگی میں انجام دیتے ہیں۔ ہم آپ سے پچھلے ے دنوں کے بارے میں سوالات پوچھیں گے آپ ان جسمانی کاموں یا مشقت کے بارے میں سوچیں جو کہ آپ نے اپنے کام، گھر کے کام، ایک جگہ سے دوسری جگہ آنے جانے کے سلسلے میں اور اپنے فارغ وقت میں سیرو تفریح، ورزش یا کھیل کود کے دوران کام کیے ہوں۔ آپ اُن تمام سخت مشقت والے کاموں کے بارے میں سوچیں جو کہ آپ نے پچھلے سات دنوں میں کئے ہوں۔ وہ سارے کام کاج جن کے کرنے سے آپکی سانس کی رفتار معمول سے بہت زیادہ تیز ہوجائے، سخت جسمانی مشقت میں آتے ہیں۔ ان کاموں کے بارے میں سوچیں جو آپ نے کم از کم 10 منٹ تک کئے ہوں۔

B6.1 گزشتہ 7 دنوں کے دوران آپ نے کتنے دن سخت مشقت والے کام کئے ہیں جیسا کہ وزنی سامان اُٹھانا، کھدائی کرنا، ورزش کرنا یا تیز رفتاری سے سائیکل چلانا۔ (اگر نہیں تو سوال نمبر B6.3 پر جائیں)

دن ہفتہ میں ☐

☐ No virgorous phsical activity

B6.2 اُن دنوں کے دوران آپ نے عموماً ایک دن میں کتنا وقت سخت جسمانی محنت والے کاموں میں صرف کیا۔

گھنٹے دن میں ☐☐

منٹ دن میں ☐☐

☐ Not sure/DK

اب آپ گزشتہ 7 دنوں کے دوران درمیانی مشقت والے کاموں یا مصروفیات کے بارے میں سوچیں۔ درمیانی مصروفیات سے مراد وہ مصروفیات ہیں جس میں درمیانی جسمانی مشقت لگتی ہو اور آپ کو معمول سے کچھ زیادہ زور سے سانس لینی پڑے۔ آپ صرف اُن جسمانی مصروفیات کے بارے میں سوچیں جو کہ آپ نے ایک وقت میں کم سے کم ۱۰ منٹ کے لئے کی ہو۔

B6.3 گزشتہ 7 دنوں کے دوران آپ نے کتنے دن درمیانہ مشقت والے کام کئے جیسا کہ ہلکا وزن اُٹھانا، عام رفتار سے سائیکل چلانا، بچوں کو گود میں اُٹھانا، پانی کا گھڑا یا بالٹی ایک جگہ سے دوسری جگہ لے جانا، اس میں چہل قدمی (ٹہلنا) شامل نہ کریں۔ (اگر نہیں تو سوال نمبر B6.5 پر جائیں)

: دن ہفتہ میں ☐

☐ No moderate Phy actv

B6.4 اُن دنوں میں آپ نے عموماً کتنا وقت ان درمیانہ مشقت والے کاموں میں صرف کئے۔

گھنٹے دن میں ☐☐

منٹ دن میں ☐☐

☐ Not sure/DK

اب آپ گزشتہ 7 دنوں کے دوران اُس وقت کے بارے میں سوچیں جو کہ آپ نے چہل قدمی میں صرف کیا۔ اس میں شامل ہے گھر اور نوکری، ایک جگہ سے دوسری کا سفر اور کوئی اور چہل قدمی (ٹہلنا) جو کہ آپ نے صرف تفریح، کھیل، ورزش یا راحت و آرام کے لئے کی ہو۔

B6.5 گزشتہ 7 دنوں کے دوران آپ نے کتنے دن کم از کم ایک وقت میں 10 منٹ تک چہل قدمی کی۔ (اگر نہیں تو سوال نمبر B6.7 پر جائیں)

دن ہفتہ میں ☐

☐ No walking

B6.6 ان دنوں میں آپ نے عموماً کتنا وقت چہل قدمی میں صرف کیا۔

یہ سوال اُس وقت کے متعلق ہے جو گزشتہ 7 دنوں کے دوران کام کے دنوں میں آپ نے بیٹھنے میں صرف کیا ہو اس میں شامل کریں وہ وقت جو کہ آپ نے صرف کیا ہو کام یا نوکری میں، گھر پر اور راحت اور آرام کے دوران، اس میں وہ وقت بھی شامل ہو سکتا ہے جو صرف کیا ہو ڈیسک پر بیٹھنے میں، دوستوں سے ملنے میں، پڑھنے میں، بیٹھ کر یا لیٹ کر ٹی وی دیکھنے میں۔

گھنٹے دن میں ☐☐

منٹ دن میں ☐☐

☐ Not sure/DK

B6.7 گزشتہ 7 دنوں میں آپ نے کام کے دنوں میں کتنا وقت بیٹھ کر گزارا۔

B6.8 اوسطاً آپ نے ایک ہفتے میں کتنے دن گھر یا گھر کے باہر درج ذیل کاموں میں گزارے؟

(اگر کوئی کام نہ کیا ہو تو جواب میں "0" لکھیں اور اگر جواب "0" نہ ہو تو گھنٹوں کے بارے میں پوچھیں)۔

کام	نمبر	days/week	hours/day
کھانا پکانا	1	☐	☐☐
گھر کی صفائی مثلاً پونچھا، جھاڑو وغیرہ لگانا۔	2	☐	☐☐
کپڑے دھونا اور استری کرنا۔	3	☐	☐☐
خریداری کرنا اور گھر کے لئے سودا لے کر آنا۔	4	☐	☐☐

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C1 Anthropometry and BP Readings

	1t Reading Time: _____	
C1.1	Have you smoked a cigarette or taken coffee or tea in the last 30 minutes?	○ Yes ○ N
C1.2	Mid arm circumference	☐☐☐ cm
C1.3	Cuff size	○ Larger ○ Extra-Larger
C1.4	Pulse (Right forearm)	☐☐☐ /min
C1.5	Systolic Blood pressure (Right arm)	☐☐☐ mmHg
C1.6	Diastolic Blood pressure (Right arm)	☐☐☐ mmHg
	2nd reading after 01 minutes	
C1.7	Pulse (Right forearm)	☐☐☐ /min
C1.8	Systolic Blood pressure (Right arm)	☐☐☐ mmHg
C1.9	Diastolic Blood pressure (Right arm)	☐☐☐ mmHg
	3rd reading after 01 minutes	
C1.10	Pulse (Right forearm)	☐☐☐ /min
C1.11	Systolic Blood pressure (Right arm)	☐☐☐ mmHg
C1.12	Diastolic Blood pressure (Right arm)	☐☐☐ mmHg
	Mean of Final 02 readings	
C1.13	Mean Systolic Blood pressure	☐☐☐ mmHg
C1.14	Mean Diastolic Blood pressure	☐☐☐ mmHg

Anthropometric measurement

C1.15	Height ----------	☐☐☐.☐ cm
C1.16	Weight ----------	☐☐☐.☐ Kg
C1.17	Hip circumference ----------	☐☐☐.☐ cm
C1.18	Waist circumference ----------	☐☐☐.☐ cm

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C2 Laboratory Tests FINAL COPY

C2.1 Fasting Glucose	☐☐☐☐
C2.2 Triglycerides	☐☐☐☐
C2.3 Cholestrol	☐☐☐☐
C2.4 HDL	☐☐☐☐
C2.5 LDL	☐☐☐☐
C2.6 AST	☐☐☐☐
C2.7 Urine Protiens	○ YES ○ NO
C2.8 Urine Microalbumin	☐☐☐☐
C2.9 Insulin	☐☐☐☐
C2.10 CRP	☐☐☐☐

CORRECTIONS

Form	Question	Correction

LANGUAGE	
1	Sindhi
2	Balochi
3	Jadgal
4	Brohi
5	Gujrati
6	Memoni
7	Kathiawari
8	Urdu
9	Punjabi
10	Pushto
11	Hindko
12	Saraiki
13	Others
99	DontKnow

Ethnic Code	
1	Sindhi
2	Balochi
3	Jadgal
4	Brohi
5	Gujrati
6	Memon
7	Kathiawari
8	Muhajir
9	Punjabi
10	Pushtoon
11	Hindko
12	Saraiki
13	Others
99	DontKnow

Relation to HH	
1	Self
2	Spouse
3	Son/Daughter
4	Son-in-Law/Daughter-in-Law
5	Grandson/ Granddaughter
6	Parent
7	Sibling
8	Other Relative
9	Other Non relative

Highest Education Level	
1	Illiterate
2	Madressa
3	Primary
4	Secondary
5	Matriculation
6	Intermidiate
7	Bachelors
8	Masters or Above
9	DontKnow

Martial Status	
1	Married
2	Divorced
3	Seperated
4	Widowed
5	Single

Employment Status	
1	Student / Too Young
2	Working for Daily Wages(cash or Kind)
3	Self-Employed
4	Working for wages and Employed
5	Unemployed
6	Physically Handicap
7	Bed-ridden
9	DontKnow

Birth Place	
1	Lyari
2	North Nazimabad
3	Karachi
4	Sindh
5	Balochistan
6	Punjab
7	NWFP
8	Northern Areas
9	British India
10	Iran
11	Afghanistan
12	Other
99	DontKnow

Delivery Location	
1	Home, unassisted
2	Home,Dai
3	Home,Trained Attendant
4	Maternity Home
5	Hospital
6	Other
9	DontKnow

Source of Treatment	
1	No treatment
2	Govt Hospital
3	Govt Dispensary
4	Pvt Hospital
5	GP
6	Homeo
7	Hakim

Who Told You the Cause of Death	
1	Doctor
2	Other Health Person
3	Self Judgement
9	Don't Know

Approval of Local Ethics Committee

REVIEW AND APPROVAL OF PREVALENCE OF DIABETES AND ASSOCIATED RISK FACTORS AMONG ADULTS 25 YEARS AND ABOVE IN URBAN KARACHI

By INSTITUTIONAL REVIEW BOARD

A: INFORMATION

Name and Address of Ethical Review Board:
Institutional Review Board
Baqai Institute of Diabetology and Endocrinology, III- B, 3/17, Nazimabad No. 3, Karachi- 74600

Study Title:
'Prevalence of Diabetes and Associated Risk Factors among Adults 25 Years and Above in Urban Karachi'.

Name and Address of the Principal Investigator:
Prof A. Samad Shera TI, SI, FRCP
Honorary President IDF
Director WHO Collaborating Centre
Secretary General DAP
5-E/3, Nazimabad, Karachi-74600
Ph: + 92-21-6616890 Email: dapkhi@cyber.net.pk

B: REVIEW

The following items have been reviewed in connection with the above study to be conducted by the above investigator:

Protocol
Informed Consent Document
Questionnaire / Patient Information Sheet

Conditionally approved (specify required modification here or in accompanying letter):

- Final Questionnaire to be submitted in local language 'Urdu' before start of study.
- Consent Form in Local Language 'Urdu'.

Date of IRB Approval: June 9, 2004

Dr. Shakil Baig
Chairman,
Institutional Review Board

INSTITUTIONAL REVIEW BOARD MEMBERS

Name	Profession	Address/Ph #
• Dr. Shakil Baig M.B.B.S., M.R.C.P.	Consultant Rheumatologist	
• Dr. Abdul Basit M.B.B.S., M.R.C.P.	Consultant Diabetologist & Endocrinologist	Baqai Institute of
• Dr. Yakoob Ahmedani M.B.B.S.,FCPS	Consultant Physician	Diabetology and
• Dr.Mohiuddin Waseem M.B.B.S,D.A.B.I.M.	Consultant Diabetologist & Endocrinologist	Endocrinology
• Dr M Zafar Iqbal Abbasi	Administrator BIDE	Ph.: 6617234-5
• Mufti Fazal Karim	Non-Organizational Member / Non-Medical Member	

9 Appendix II (Questionnaire of Second Study)

Diabetes Prevention Study
Diabetic Association of Pakistan
Baqai Institute of Diabetology and Endocrinology
University of Oslo
Questionnaire

1.1 Date: ☐☐ ☐☐ ☐☐☐☐ 1.2 : Registration No: ☐☐☐☐☐

1.3 Name: ☐☐☐☐☐☐☐☐ D/o ☐☐☐☐☐☐

1.4 Date of Birth ☐☐ ☐☐ ☐☐☐☐ 1.5 Age: (in years) ☐☐☐

1.6 Sex: Male= 1, Female= 2. 1.7 Marital Status: Married=1, Single =2, Widow=3

1.8 Address: ☐

District ☐

1.9 Phone Number Home: ☐☐☐☐☐☐☐☐

Mobile: ☐☐☐☐☐☐☐☐

Date of visit	Type of visit	Advisor	Focus
d d m m y y	1. Individual 2. Group 3. Short contact (phone, letter, e-mail etc.)	1. Nurse 2. Physician 3. Physiotherapist 4. Dietitian 5. Psychologist 6. Other	1. Diet / weight loss 2. Exercise 3. Smoking withdrawal 4. Other

1.10 Occupation:

Administrative/Professional =1, Business=2, Skilled Labour=3, Manual Labour=4

Home Duties =5,Unemployed=6, Pensioner=7, Others =8 ☐☐☐☐☐☐

1.11 Education :

Illiterate =1 Only Read & Write=2 Primary =3 Secondary =4, Matric/ SSC =5 , Inter/HSC=6, Graduate=7, Specialty=8 (specify) ☐☐☐☐☐☐

1.11b Education in Number of Years ☐☐

1.12 Socio-economic History: Are you Earner = 1 or Dependent = 2

Total family monthly income from all sources

Rs.< 5000/- =1. Rs. 5000 – 10,000/- =2, Rs. 10,000 – 20,000/- = 3, Rs. 20,000 – 30,000/- = 4,
> Rs. 30,000/- = 5

No. of Earners ☐ No. of Dependents ☐

1.13 Community:

Mohajir = 1, Punjabi = 2, Sindh = 3, Pathan = 4, Balochi = 5, Makrani=6, Memon = 7, Others (Specify) = 8 ☐☐☐☐☐☐

2 Personal History

Family History in first degree relative (Parents, Siblings & Children)

Serial	Disease	Subjects	No =1, Yes =2,
1	Diabetes		
2	Hypertension		
3	Ischemic Heart Disease		
4	Stroke		
5	Others		

2.2 Any addiction: Niswar = 1, Cigarettes = 2, Biri = 3, Chews Tobacco = 4, Huqqa = 5, Alcohol = 6, Other = 7 ☐☐☐☐☐

3 History of past illness:

Please circle correct response

3.1 Has a doctor ever told you that you have; If yes are you currently, Medicine name taking any medications

High blood pressure.	Yes	No	Yes	No	_____
Angina	Yes	No	Yes	No	_____
Heart Attack	Yes	No	Yes	No	_____
Stroke.	Yes	No	Yes	No	_____
Foot ulceration.		Yes	No	Yes	No _____
Hyperlipidemia	Yes	No	Yes	No	_____
Claudation	Yes	No	Yes	No	_____
Depression	Yes	No	Yes	No	_____
Others Specify	Yes	No	Yes	No	_____

Obstetric History (Women Only)

Number of Live Births _____ Number of Still Births _____

Number of miscarriages _____ Number of abortions _____

4 Blood Glucose Result Lab Serial No_____

4.1 How many hours since last food or drink, except water? ***Hours =*** ☐

4.2 Fasting Blood Glucose Levels = ☐

4.3

Time of Glucose Drink = ☐☐☐☐ ***Hours, minutes.Time of 2nd Sample*** ☐☐☐☐

4.4 Two hours Blood Glucose levels = ☐

Initials _____

B Physical Examination

5.1 Height (cm) ____ cm

5.2 Weight (kg) ____ , __ kg

5.3. BMI (kg/m^2) ____ , __

5.4 Waist circumference (cm) ____ cm

5.5. Hip circumference (cm) ____ cm

5.6 WHRatio ____ , __

6. Blood pressure (mmHg)

6.1 First measurement (systolic/diastolic) ____ / ____

6.2 Second measurement (systolic/diastolic) ____ / ____

6.3 Third measurement (systolic/diastolic) ____ / ____

		Right	Left
7	Visual Acuity		
8	***Eye Examination (Fundoscopy)***		

(Code of 8.1 & 8.2: Nil=0, 1 to 5=1, 6 to 10=2, 11+ =3, Retina not visible=9)

8.1	Microdots	0 1 2 3 9	0 1 2 3 9
8.2	Blot Haemorrhages	0 1 2 3 9	0 1 2 3 9

(Code of 8.3, 8.4 & 8.5 : Absent = 0, Present = 1, Retina not visible = 9)

8.3	Exudates (hard)	0 1 9	0 1 9
8.4	Exudates (soft)	0 1 9	0 1 9
8.5	Vitreous Haemorrhage	0 1 9	0 1 9

(Code of 8.6: Nil=0, Peripheral=1, Disc=2, RP=3, Retina not seen=9)

8.6	New vessels	0 1 2 3 9	0 1 2 3 9

(Code of 8.7 : Nil=0, mild=1, Retina not seen clearly=2 ,lens removed=3)

8.7	Cataracts	0 1 2 3	0 1 2 3

9 Limb Examination

9.1 Pulses

(Code of 9.1: normal =0, diminshed =1, absent =2, amputation = 9)

9.1a	Femoral	0 1 2 9	0 1 2 9
9.1b	Popliteal	0 1 2 9	0 1 2 9
9.1c	Dorsalis pedis	0 1 2 9	0 1 2 9
9.1d	Tibialis posterior	0 1 2 9	0 1 2 9

9.2 Sensation

(Code of 9.2: normal=0, diminshed=1, absent=2, amputation=9)

9.2a	Touch with 10gm monofilament	0 1 2 9	0 1 2 9
9.2b	Vibration with 128 Hz tuning fork	0 1 2 9	0 1 2 9

9.3 Reflexes

(Code of 9.3 : present =0,diminshed = 1, absent=2,amputation = 9)

9.3a	Knee	0 1 2 9	0 1 2 9
9.3b	Ankle	0 1 2 9	0 1 2 9

Food Frequency Questionnaire						Date of Visit		Date of Visit		Date of Visit	
	Quantity	/Day	/wk	/mth	Never<1 Mth	Recommend	Assess	Recommend	Assess	Recommend	Assess
Braek fast											
Bread / Chappati *											
Paratha *											
Papey *											
Biscuits *											
Bun *											
Egg *											
Egg whites *											
Jam / jellies ***											
Margarine ***											
Tea **											
Milk **											
Anyother / nothing											
Mid morning											
Fruit (with or without skin) *											
Biscuits *											
Chanay /lobia/lentils **											
pop-corn **											
bakery biscuits **											
Anyother /nothing **											
Lunch											
Salad **											
Chappati */ Rice**											
vegetable(cooked) **											
Daal **											
Meat *											
fish/chicken *											
organ meat *											
Anyother /nothing											

Food Frequency Questionnaire						**Date of Visit**		**Date of Visit**		**Date of Visit**	
	Quantity	**/Day**	**/wk**	**/mth**	**Never<1 Mth**	**Recommend**	**Assess**	**Recommend**	**Assess**	**Recommend**	**Assess**
Tea time											
Biscuits *											
fried items *											
Tea **											
Anyother /nothing											
Dinner											
Salad **											
Chappati * Rice **											
vegetable(cooked) **											
Daal **											
Meat *											
fish/chicken *											
orgen meat *											
Anyother /nothing											
Bed time											
Milk **											
Fruit (with or without skin) *											
Anyother / nothing											
Total Calories											
Total Fat											
Type of Fat											
Eating out											
Refined CHO											

* In numbers
** In cups
*** In teaspoons

Physical Activity			
Questions		Response	Code
Activity at work			
1	Does your work involve vigorous-intensity activity that causes large increases in breathing or heart like [carrying or lifting heavy loads, digging or construction work] for at least 10 minutes continuously?	Yes 1 No 2 If No, go to P 4	P1
2	In a typical week, on how many days do you do vigorous-intensity activities as part of your work?	Number of days ☐☐	P2
3	How much time do you spend doing vigorous-intensity activities at work on a typical day?	Hours : minutes ☐☐ ☐☐	P3 (a-b)
4	Does your work involve moderate-intensity activity that causes small increases in breathing or heart rate such as brisk walking [or carrying light loads] for at least 10 minutes continuously?	Yes 1 No 2 If No, go to P 7	P4
5	In a typical week, on how many days do you do moderate-intensity activities as part of your work?	Number of days ☐	P5
6	How much time do you spend doing moderate-intensity activities at work on a typical day?	Hours : minutes ☐☐ ☐☐	P6 (a-b)
Travel to and from places			
7	Do you walk or use a bicycle (pedal cycle) for at least 10 minutes continuously to get to and from places?	Yes 1 No 2 If No, go to P10	P7
8	In a typical week, on how many days do you walk or bicycle for at least 10 minutes continuously to get to and from places?	Number of days ☐	P8
9	How much time do you spend walking or bicycling for travel on a typical day?	Hours : minutes ☐☐ ☐☐	P9
Recreational activities			
10	Do you do any vigorous-intensity sports, fitness or recreational (leisure) activities that cause large increases in breathing or heart rate [running or football,] for at least 10 minutes continuously?	Yes 1 No 2 If No, go to P13	P10
11	In a typical week, on how many days do you do vigorous-intensity sports, fitness or (leisure) activities?	Number of days ☐	P11
12	How much time do you spend doing vigorous-intensity sports, fitness or recreational activities on a typical day?	Hours : minutes ☐☐ ☐☐	P12
13	Do you do any moderate-intensity sports, fitness or recreational (leisure) activities that causes a small increase in breathing or heart rate such as brisk walking, (cycle, swimming, volleyball) for at least 10 minutes continuously?	Yes 1 No 2 If No, go to P16	P13
14	In a typical week, on how many days do you do moderate-intensity sports, fitness or recreational (leisure) activities?	Number of days ☐	P14
15	How much time do you spend doing moderate-intensity sports, fitness or recreational (leisure) activities on a typical days?	Hours : minutes ☐☐ ☐☐	P15
Sedentary behaviour			
16	How much time do you usually spend sitting or reclining on a typical day?	Hours : minutes ☐☐ ☐☐	P16

Physical Activity			
Questions		Response	Code
Activity at work			
1	Does your work involve vigorous-intensity activity that causes large increases in breathing or heart like [carrying or lifting heavy loads, digging or construction work] for at least 10 minutes continuously?	Yes 1 No 2 If No, go to P 4	P1
2	In a typical week, on how many days do you do vigorous-intensity activities as part of your work?	Number of days ☐☐	P2
3	How much time do you spend doing vigorous-intensity activities at work on a typical day?	Hours : minutes ☐☐ ☐☐	P3 (a-b)
4	Does your work involve moderate-intensity activity that causes small increases in breathing or heart rate such as brisk walking [or carrying light loads] for at least 10 minutes continuously?	Yes 1 No 2 If No, go to P 7	P4
5	In a typical week, on how many days do you do moderate-intensity activities as part of your work?	Number of days ☐	P5
6	How much time do you spend doing moderate-intensity activities at work on a typical day?	Hours : minutes ☐☐ ☐☐	P6 (a-b)
Travel to and from places			
7	Do you walk or use a bicycle (pedal cycle) for at least 10 minutes continuously to get to and from places?	Yes 1 No 2 If No, go to P10	P7
8	In a typical week, on how many days do you walk or bicycle for at least 10 minutes continuously to get to and from places?	Number of days ☐	P8
9	How much time do you spend walking or bicycling for travel on a typical day?	Hours : minutes ☐☐ ☐☐	P9
Recreational activities			
10	Do you do any vigorous-intensity sports, fitness or recreational (leisure) activities that cause large increases in breathing or heart rate [running or football,] for at least 10 minutes continuously?	Yes 1 No 2 If No, go to P13	P10
11	In a typical week, on how many days do you do vigorous-intensity sports, fitness or (leisure) activities?	Number of days ☐	P11
12	How much time do you spend doing vigorous-intensity sports, fitness or recreational activities on a typical day?	Hours : minutes ☐☐ ☐☐	P12
13	Do you do any moderate-intensity sports, fitness or recreational (leisure) activities that causes a small increase in breathing or heart rate such as brisk walking, (cycle, swimming, volleyball) for at least 10 minutes continuously?	Yes 1 No 2 If No, go to P16	P13
14	In a typical week, on how many days do you do moderate-intensity sports, fitness or recreational (leisure) activities?	Number of days ☐	P14
15	How much time do you spend doing moderate-intensity sports, fitness or recreational (leisure) activities on a typical days?	Hours : minutes ☐☐ ☐☐	P15
Sedentary behaviour			
16	How much time do you usually spend sitting or reclining on a typical day?	Hours : minutes ☐☐ ☐☐	P16

PHYSICAL ACTIVITY RECOMMENDATION Registration No.

- **FLEXIBILITY EXERCISE:**

Date					
1)					
2)					
3)					
4)					

PHYSICAL ACTIVITY RECOMMENDATION Registration No.

- **STRENGTH TRAINING:**

Date					
1)					
2)					
3)					
4)					

PHYSICAL ACTIVITY RECOMMENDATION Registration No.

- **CARDIO RESPIRATORY EXERCISES:**

Date					
1)					
2)					
3)					
4)					

Lab Investigations *Registration No:* _____

Date	0 months	9 months*	18 months	Remarks
OGTT – Fasting BS mg/dl				
OGTT – 2 Hrs Postprandial BS mg/dl				
Fasting Total Lipids mg/dl				
Total Cholesterol mg/dl				
Triglyceride mg/dl				
HDL mg/dl				
LDL mg/dl				
Fasting Insulin Levels				
HbA1c %				

Last Visit

B Physical Examination

5.1 Height (cm) ___ cm

5.2 Weight (kg) ___ , ___ kg

5.3. BMI (kg/m^2) ___ , ___

5.4 Waist circumference (cm) ___ cm

5.5. Hip circumference (cm) ___ cm

5.6 WHRatio ___ , ___

6. Blood pressure (mmHg)

6.1 First measurement (systolic/diastolic) ___ / ___

6.2 Second measurement (systolic/diastolic) ___ / ___

6.3 Third measurement (systolic/diastolic) ___ / ___

Last Visit	Right	Left
7 Visual Acuity		
8 Eye Examination (Fundoscopy)	☐	☐

(Code of 8.1 & 8.2: Nil=0, 1 to 5=1, 6 to 10=2, 11+ =3, Retina not visible=9)

		Right	Left
8.1	Microdots	0 1 2 3 9	0 1 2 3 9
8.2	Blot Haemorrhages	0 1 2 3 9	0 1 2 3 9

(Code of 8.3, 8.4 & 8.5 : Absent = 0, Present = 1, Retina not visible = 9)

		Right	Left
8.3	Exudates (hard)	0 1 9	0 1 9
8.4	Exudates (soft)	0 1 9	0 1 9
8.5	Vitreous Haemorrhage	0 1 9	0 1 9

(Code of 8.6: Nil=0, Peripheral=1, Disc=2, RP=3, Retina not seen=9)

		Right	Left
8.6	New vessels	0 1 2 3 9	0 1 2 3 9

(Code of 8.7 : Nil=0, mild=1, Retina not seen clearly=2 ,lens removed=3)

		Right	Left
8.7	Cataracts	0 1 2 3	0 1 2 3

9 Limb Examination

9.1 Pulses

(Code of 9.1: normal =0, diminshed =1, absent =2, amputation = 9)

9.1a	Femoral	0 1 2 9	0 1 2 9
9.1b	Popliteal	0 1 2 9	0 1 2 9
9.1c	Dorsalis pedis	0 1 2 9	0 1 2 9
9.1d	Tibialis posterior	0 1 2 9	0 1 2 9

9.2 Sensation

(Code of 9.2: normal=0, diminshed=1, absent=2, amputation=9)

9.2a	Touch with 10gm monofilament	0 1 2 9	0 1 2 9
9.2b	Vibration with 128 Hz tuning fork	0 1 2 9	0 1 2 9

9.3 Reflexes

(Code of 9.3 : present =0,diminshed = 1, absent=2,amputation = 9)

9.3a	Knee	0 1 2 9	0 1 2 9
9.3b	Ankle	0 1 2 9	0 1 2 9

Date	Weight	
B.P	Pulse	
Treatment		
Diet		

Date	Weight	
B.P	Pulse	
Treatment		
Diet		

Date	Weight	
B.P	Pulse	
Treatment		
Diet		

Informed Consent Form

You are being invited to participate in a research study (PPS). This Form is designed to provide you with information about the study. The investigators or representative describes this study to you and answer any of your questions.

Title of project: *Impact of intervention for the prevention of Type 2 diabetes: (a randomized high-risk population based study in Pakistan and Bangladesh)*

Investigator(s):_____

Address: _____

Phone No._____ CO-Investigator(s) _____

This is to certify that I, _____, hereby agree to participate as a volunteer in an authorized research project.

I understand the purpose of this research as mentioned above. The procedure involves evaluating subjects for impaired glucose tolerance according to Oral Glucose Tolerance test and enrolling them in an intervention study to prevent them from diabetes in the future. The duration of participation will be 18 months.
I understand that I will be provided physical activity and dietary advice during this period. Also my weight and dietary habits will be continuously monitored during follow-ups.
I may be given "Metformin" for the duration of the study according to selection criteria.
Benefits of participating in project may include: Obtaining optimal control of Blood Sugars and trying to prevent from progression to diabetes. Reduction in weight and increase in physical activity under professional supervision will also be achieved.
I understand that all the information which is obtained from me will be confidential in an appropriate manner.
Participation is voluntary and I understand that I am free to refuse to participate in a procedure or to refuse to answer any question at any time without prejudice to me. I understand that I am free to withdraw my consent and to withdraw from the study any time without prejudice to me.
I understand that the research investigators named above will answer any of my questions about the research procedures, my rights as a subject and research-related injuries time.

I understand that I will be given a copy of this consent form if I so request. ☐

Name and signature of participant or responsible Agent / Date.

Note:-If you have any questions or complaints about the informed consent process or policy, please contact investigator(s). **THANK YOU!**

﴿تحریری رضامندی کا فارم﴾

ہم آپ کو اپنی تحقیق میں حصہ لینے کی دعوت دیتے ہیں

۔یہ فارم آپ کو اس تحقیق کے بارے میں معلومات فراہم کرنے کے لیے ترتیب دیا گیا ہے۔ ہمارا محقق آپ کو اس تحقیق کی تفصیلات سے آگاہ کرے گا۔

تحقیق کا عنوان: ۔غذا اور ورزش کے ذریعے ذیابیطس سے بچاؤ (پاکستان اور بنگلہ دیش کی مشترکہ تحقیق)

تحقیق:

خط و کتابت کے لیے پتہ: ٹیلی فون نمبر:

معاون تحقیق:

خط و کتابت کے لیے پتہ: ٹیلی فون نمبر:

معاون شعبہ:

خط و کتابت کے لیے پتہ: ٹیلی فون نمبر:

میں۔۔۔۔۔۔۔۔۔۔۔۔کے تعاون سے شروع کی گئی تحقیق میں بحیثیت رضا کار حصہ لینے کا عہد کرتا، کرتی ہوں۔

میں سمجھتا، سمجھتی ہوں کہ اس تحقیق کا مقصد جیسے کہ اوپر دیا گیا ہے کہ اس تحقیق کے ذریعے جن افراد میں ذیابیطس ہونے کے قوی امکانات ہوں، جن افراد کا وزن زیادہ ہو، یا موروثی وجہ سے شکر ہونے کے امکانات زیادہ ہو۔ ان افراد کے لیے ۱۸ مہینے کی تحقیق کے ذریعہ ذیابیطس ہونے سے بچانا اس تحقیق کا مقصد ہے۔

میں سمجھتا، سمجھتی ہوں کہ مجھ کو جسمانی مشقت اور غذائی تجاویز دی جائیں گی۔ اس تحقیق کے دورانیہ میں پابندی سے میرا وزن اور غذا کا تجزیہ کیا جائے گا۔

ہوسکتا ہے کہ مجھ کو Metformin تجویز کی جائے جب تک یہ تحقیق جاری ہے اور اگر مجھ کو میرے ڈاکٹر نے تجویز کی ہے۔

اس تحقیق میں شرکت کے فوائد مندرجہ ذیل ہیں:

۱۔خون میں شکر کی مقدار کا اچھا کنٹرول۔

۲۔آئندہ شکر نہ ہونے سے بچاؤ کی کوشش۔

۳۔صحیح طریقے سے وزن میں کمی ڈاکٹر کی تجویز کے مطابق اور بہترین جسمانی کارکردگی کا حصول۔

میں سمجھتا، سمجھتی ہوں کہ جس تحقیق کا نام اوپر درج کیا گیا ہے وہ محض میرے ذاتی حقوق اور تحقیق سے متعلق کسی بھی نقصان کے بارے میں ہے سوال کا جواب دہ ہوگا۔

میں سمجھتا، سمجھتی ہوں کہ میری درخواست پر مجھے اس فارم کی کاپی دی جائے گی۔

شرکت کرنے والے شخص کا نام۔۔۔۔۔۔۔۔۔۔۔۔۔۔۔۔۔۔۔۔۔۔۔۔۔۔

شرکت کرنے والے شخص کے دستخط۔۔۔۔۔۔۔۔۔۔۔۔۔۔۔۔۔۔۔۔۔۔۔۔۔۔

نوٹ: اگر آپ کو تحریری رضامندی کے فارم یا تحقیق کی پالیسی کے بارے میں کوئی بھی سوال یا شکایت ہو تو محقق سے رجوع کریں۔

شکریہ۔

10 Appendix III (Papers 1 – 4)

METABOLIC SYNDROME AND RELATED DISORDERS
Volume 7, Number 2, 2009

Pp. 119–124
DOI: 10.1089/met.2008.0055

Prevalence of Metabolic Syndrome in Urban Pakistan (Karachi): Comparison of Newly Proposed International Diabetes Federation and Modified Adult Treatment Panel III Criteria

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Abstract

The clustering of central obesity, dyslipidemia, hypertension, and hyperglycemia known as metabolic syndrome has been associated with a two- to three-fold increase in type 2 diabetes (T2DM) and cardiovascular disease (CVD). It is recognized that the features of the metabolic syndrome can be present 10 years preceding T2DM and CVD. The objective of our study was to determine the prevalence of metabolic syndrome in adults aged 25 years and older from an urban population of Karachi, Pakistan, according to the International Diabetes Federation (IDF) definition and modified Adult Treatment Panel III (ATP III) criteria. This study involved a survey conducted from July, 2004, to December, 2004, by generating a computerized random sample of households in Lyari Town using a geographical imaging system (GIS). Out of the 85,520 households, 532 households were randomly selected and 867 adults ≥25 years old consented to take part in the survey; 363 of these subjects gave blood samples. The prevalence of diabetes was 9.4%, whereas 5.6% had impaired fasting glucose (abnormal glucose tolerance 15%). The prevalence of metabolic syndrome according to the IDF definition and modified ATP III criteria was 34.8% and 49%, respectively. Inclusion of modified waist circumference and specific body mass index (BMI) cut offs for Asians may help predict metabolic syndrome at an early stage. High prevalence of metabolic syndrome was identified irrespective of the definition applied in this population. This may call for immediate action to halt the accelerating risk of diabetes and CVD that would lead to a possible unparalleled rise in the cost of health care and human suffering.

Introduction

The modern era has seen the rise of computerization and mechanization, with improved transport resulting in changes in lifestyle from active to sedentary and thus making an enormous impact on human health.[1] The rise in metabolic syndrome has been partly related to the achievements in public health during the 20th century, with people living longer owing to elimination of many of the communicable diseases.[2]

Over the last 20 years, focus on the metabolic syndrome has gradually increased, and studies have shown that the prevalence of metabolic syndrome is steadily increasing in all populations worldwide, recognizing this as one of the major global public health challenges of recent times.[3] The

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high prevalence of metabolic syndrome and cardiovascular disease (CVD) risk factors have been reported in South Asians.[4–8] Although more than one fifth of the world population lives in South Asia, very few studies have been done on metabolic syndrome in this part of the world. Amongst those in India, the prevalence rates of metabolic syndrome were reported to be higher than 40%.[4] It is estimated that a population with metabolic syndrome is three times as likely to have and twice as likely to die from a heart attack or stroke compared to people without the syndrome.[9] In addition, people with metabolic syndrome have a five-fold greater risk of developing type 2 diabetes (T2DM).[10] We looked at the prevalence of Metabolic Syndrome according to International Diabetes Federation (IDF) and Modified Adult Treatment Panel III (ATPIII) criterions as given in Table 1.[10,11]

Studies have shown a high prevalence of T2DM and CVD in South Asians.[7,8,12,13] Very few studies have looked at the prevalence of metabolic syndrome in the general population in Pakistan to identify the potential for prevention of life-threatening diseases like diabetes and CVD. However, a few small-scale studies have been conducted. Such studies conducted in hospital patients have shown a prevalence rate of 44%[4]; another study conducted amongst diabetic patients showed a prevalence of metabolic syndrome of 46%.[14]

These studies were all specific, high-risk group-based studies. To the best of our knowledge, only one community-based epidemiological study on the prevalence of metabolic syndrome has been reported from a rural area of Pakistan.[15] According to International Diabetes Federation (IDF) and Adult Treatment Panel III (ATP III) definition, 40% and 31% had metabolic syndrome, respectively. Hence the study reported here is the first community-based prevalence survey of metabolic syndrome in an urban population of Pakistan. Furthermore, we have also examined the concordances between the IDF definition and modified ATP III criteria for metabolic syndrome.

Table 1. Diagnostic Criteria for the Metabolic Syndrome from the International Diabetes Federation (IDF)[10] and American Heart Association (AHA)/National Heart, Lung, and Blood Institute (NHLBI)[11]

IDF clinical criteria for metabolic syndrome		*AHA/NHLBI diagnostic criteria for metabolic syndrome*	
Measure (central obesity plus any two of five other criteria constitute a diagnosis of metabolic syndrome)	*Categorical cut points*	*Measure (any three of the five criteria below constitute a diagnosis of metabolic syndrome)*	*Categorical cut points*
Central obesity	Waist circumference ethnicity specific For South Asians: ≥90 cm in men, ≥80 cm in women	Elevated waist circumference	General U.S. population: ≥102 cm (≥40 in.) in men, ≥88 cm (≥35 in.) in women; lower cut points for insulin-resistant individuals or ethnic groups (for South Asians: ≥90 cm in men, ≥80 cm in women)
Raised triglycerides	>150 mg/dL (1.7 mmol/L) or on specific treatment for this lipid disorder	Elevated triglycerides	≥150 mg/dL (1.7 mmol/L) or on drug treatment for elevated triglycerides
Reduced high-density lipoprotein cholesterol	<40 mg/dL (1.03 mmol/L) in men, <50 mg/dL (1.29 mmol/L) in women or on specific treatment for this lipid abnormality	Reduced high-density lipoprotein cholesterol	<40 mg/dL (1.03 mmol/L) in men, <50 mg/dL (1.29 mmol/L) in women
Raised blood pressure	≥130 mmHg systolic blood pressure or ≥85 mmHg diastolic blood pressure or on treatment for previously diagnosed hypertension	Elevated blood pressure	≥130 mmHg systolic blood pressure or ≥85 mmHg diastolic blood pressure or on drug treatment for hypertension
Raised fasting glucose	Fasting plasma glucose ≥100 mg/d1L (5.6 mmol/L) or previously diagnosed type 2 diabetes	Raised fasting glucose	Fasting plasma glucose ≥100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes

Materials and Methods

Study area and population

The survey activities were conducted over a period of 6 months from July, 2004, to December, 2004. The Lyari Town Geographical Information System (GIS) was made by the Population Census Office, Statistics Bureau Sindh, and a research organization to define the geopolitical boundaries and population density of Lyari Town (estimated 2004 population, 700,000). This was done by dynamically linking the national census database to a purpose-built GIS. This GIS ascribed unique identification numbers to 85,520 households, which was the initial criteria for studying the prevalence of metabolic syndrome among randomly selected households in Lyari.

The rationale for choosing Lyari Town for this study was that its residents comprise a multiethnic community that includes the major ethnic groups found in Pakistan. There is similarly a wide spectrum of socioeconomic groups in the area that could possibly be representative of the general population.

Methodology

The ethical approval for this survey was given by Institutional Review Board (IRB) of Baqai Institute of Diabetology and Endocrinology. The survey activities were divided into two phases, the household interview plus physical examination and blood sample collection. Amongst the initial households selected, 532 households were randomly selected through the GIS software and maps. These households were then generated into nine field segments, which were the responsibility of nine field teams. A field team comprised of one or two medical students, a female health worker, and a male health worker. All teams and surveyors were supervised by a medical doctor acting as the field coordinator.

If members of a selected household were absent or refused to participate, then the third door to the right of that house (while standing facing the door of the original house) was approached and consent to participate was sought. In case of further denial or absence, the next consecutive door to the right was selected. All adults 25 years and older were invited to participate after providing signed consent. In the case of illiterate participants, the consent form was read out to them and a thumbprint was procured in the presence of a household member or neighbor as witness.

By following this procedure, a total of 871 persons >25 years were approached, out of which 867 persons participated in the survey (response rate, 99.5%). These people were interviewed by the field teams, and their anthropometric measures were performed and blood samples were collected. Of these, 363 persons gave blood, producing a response rate of 42% for blood collection.

Anthropometry

Anthropometric and demographic information was collected during interview. Weight, height, waist, and hip circumference were measured with the participants in standing position wearing light clothes and no shoes. The weight was taken to the nearest 0.1 kg by a digital bathroom scale and height was taken to the 0.1 cm. Body mass index (BMI) was calculated as a ratio of weight (kg) to height in meters squared. Waist circumference was measured at the minimum circumference between the lower border of the ribs and iliac crest on the midaxillary line, and hip circumference was measured at the greatest protrusion of the buttocks just below the iliac crest The measurements were taken in centimeters, and the waist-to-hip ratio (WHR) was calculated as waist/hip circumference.

Blood pressure was measured with a special precaution to reduce the variation of blood pressure value with resting values: individuals were requested to take 10 minutes rest at a sitting position before measuring the blood pressure. We used standard cuffs for an adult-fitted mercury sphygmomanometer for all individuals to minimize the difference. Two blood pressure readings were taken, and a mean value was used for the final measurements.

Laboratory assays

At the end of the household visit, all adults 25 years and older were asked to undertake an 8-hour fast for blood tests (fasting blood glucose and lipid profile) that was collected at home on weekends. Within 1 hour of blood collection, the samples were centrifuged and separated. All selected parameters of blood lipids (total cholesterol, triglycerides, high-density lipoprotein cholesterol [HDL-C] and low-density cholesterol [LDL-C]) and blood glucose estimation were performed using a Vitalab Selectra autoanalyzer. Fasting blood glucose and lipid profiles were done by the glucose oxidase GOD PAP method and cholesterol CHOD PAP method, respectively. Fasting insulin levels were measured, but these will be presented elsewhere.

Criteria for metabolic syndrome

Diagnostic criteria for the metabolic syndrome were from the IDF[10] and American Heart Association (AHA)/National Heart, Lung, and Blood Institute (NHLBI) (Table 1).[11]

Statistical analysis

All data were recorded on forms developed using TeleForm® Version 6.01, an optical character recognition software. Later this data was converted into the software package Statistical Package for Social Sciences (SPSS, version 11.5) for analysis. The prevalence of metabolic syndrome was determined by simple percentages and with 95% confidence intervals (CIs). For group comparisons, the chi-square test was performed; the Student *t*-test was performed for continuous variables. A P value of <0.05 was considered statistically significant. The age-specific distribution of prevalence of metabolic syndrome was calculated for men and women separately and described in percentages. A kappa test was done to examine the agreement among the definitions. All P values presented are two tailed.

Results

Description of anthropometric and biochemical parameters are provided in Table 2. Female subjects were younger but had higher BMI values and total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) levels. Males were older and had higher waist circumference,

Table 2. Means of Anthropometric and Biochemical Parameters of Subjects ($N = 363$)

	Male *mean ± SD*	*Female* *mean ± SD*	*Total* *mean ± SD*
Age (years)	45.1 ± 15.7	38.8 ± 12.8	40.8 ± 14.1
BMI (kg/m^2)	23.9 ± 7.2	26.0 ± 7.1	25.4 ± 7.2
Waist-to-hip ratio	0.94 ± 0.11	0.91 ± 0.16	0.92 ± 0.15
Waist circumference (cm)	89.5 ± 16.0	87.8 ± 15.8	88.4 ± 15.8
Systolic blood pressure (mmHg)	127.4 ± 18.6	124.3 ± 19.6	125.2 ± 19.3
Diastolic blood pressure (mmHg)	84.3 ± 11.8	79.9 ± 13.7	81.2 ± 13.3
Fasting plasma glucose (mg/dL)	86.7 ± 21.7	86.6 ± 23.2	86.6 ± 22.7
Cholesterol (mg/dL)	175.9 ± 42.6	180.7 ± 44.6	179.2 ± 43.9
Triglycerides (mg/dL)	158.9 ± 105.2	135.2 ± 70.2	142.6 ± 83.3
Low-density lipoprotein (mg/dL)	110.7 ± 28.8	116.2 ± 33.0	114.5 ± 31.8
High-density lipoprotein (mg/dL)	37.1 ± 10.4	43.2 ± 12.4	41.3 ± 12.2

Abbreviations: SD, standard deviation; BMI, body mass index.

blood pressure, and triglyceride values. Approximately 30% of the subjects had higher total cholesterol, triglycerides, and LDL levels, as shown in Table 3. A total of 70% had low HDL levels, which are typical of the data presented in Europe from the Indian subcontinent. The revalence of diabetes was 9.4%, whereas 5.6% had impaired fasting glucose (abnormal glucose tolerance 15%).

The overall prevalence of metabolic syndrome was 34.8% and 49% according to IDF and modified ATP III classifications, respectively (Table 4). The prevalence rates of the metabolic syndrome increased with increasing age. Significant differences in the prevalence of metabolic syndrome with respect to age groups were found only in females (P values <0.05) (Table 4). There was fairly good agreement between the two definitions of metabolic syndrome, with a kappa value of 0.67. All of those ($n = 120$) who were classified as having metabolic syndrome following IDF criteria were sustained according to the modified ATP III criteria.

Discussion

Our study showed a very high prevalence of the metabolic syndrome according to IDF and modified ATP III classifications in this population. The prevalence increased with age for both sexes using both definitions in our population. This trend was also seen in other studies done in South Asian and U.S. populations.[4,16–18] One possible reason for the observed higher rate of metabolic syndrome in this population is the high rate of obesity following the Asian cut-off criteria.[19]

In addition, lower waist circumference applied with modified ATP III criteria instead of the original cut off in our study may have also increased the prevalence of metabolic syndrome. However, our data are consistent with studies done in Indian, Bangladeshi, and Chinese populations.[4,17,20] The prevalence rate was relatively higher following modified ATP III criteria in our study population. Other studies in the region also showed higher prevalence rates ranging from 35.2% to 41%.[4,21] A study conducted in older subjects in Pakistan (aged 40 years and above) showed a prevalence rate of 45.9% in males and 57.2% in females.[22]

The reported prevalence rate from Chennai, India, was 26% compared to our prevalence of 34.8% following IDF criteria,[23] whereas a study done in rural Pakistan showed a prevalence of 40%.[5] The prevalence of metabolic syndrome was also seen to increase with advancing age. This was also

Table 3. Percentage of Biochemical Risk Factors for Metabolic Syndrome

Variable	*Males* *n (%)* *95% CI*	*Females* *n (%)* *95% CI*	*Total* *n (%)* *95% CI*
Cholesterol >200 mg/dL	26/95 (26.8) (17.99–35.62)	68/216 (31.48) (25.28–37.67)	94/313 (30.0) (24.92–54.92)
Triglycerides >150 mg/dL	35/94 (37.23) (27.46–47.00)	57/208 (27.4) (21.34–33.46)	92/302 (30.5) (25.30–55.80)
Low-density lipoprotein >130 mg/dL	25/97 (25.77) (17.06–34.47)	63/216 (29.16) (64.77–35.22%)	88/313 (28.1) (23.12–51.22)
High-density lipoprotein <40 mg/dL for males, <50 mg/dL for females	63/96 (65.62) (56.12–75.12)	153/216 (70.83) (64.77–76.89)	216/312 (69.2) (64.07–133.27)

Abbreviation: CI, confidence interval.

Table 4. Prevalence of 95% CI of Metabolic Syndrome Using Modified ATP III and IDF Definition by Age and Sex

Age group	*n*	*ATP II* %	*IDF* %
Overall	363	49 (43.8–54.1)	34.8 (29.65–39.94)
Male			
25–34	37	54.1 (37.98–70.21)	31.3 (15.18–47.41)
35–44	30	56.7 (38.8–74.59)	21.4 (3.50–39.29)
45–54	15	53.3 (27.99–78.6)	46.7 (21.39–72.00)
>55	35	57.2 (40.80–73.6)	34.4 (18.66–50.13)
Total	117	55.6 (46.53–64.66)	31.8 (22.73–40.86)
Female			
25–34	107	27.1 (17.62–36.57)	14.9 (5.42–24.37)
35–44	68	51.5 (39.61–63.38)	37.3 (25.41–49.18)
45–54	31	58.1 (40.49–78.7)	60.0 (42.39–77.6)
>55	40	76.8 (63.71–89.88)	69.05 (54.72–83.37)
Total	246	45.9 (39.65–52.14)	36.1 (29.85–42.34)

Abbreviations: CI, confidence interval; ATP III, Adult Treatment Panel III; IDF, International Diabetes Federation.

observed in other studies.[4,15,24–28] The prevalence rate of metabolic syndrome was slightly higher in female subjects by IDF definition, whereas this was higher in males according to the modified ATP III definition.

The significant higher prevalence of metabolic syndrome in Pakistani women by IDF definition is likely to have been influenced by higher rates of central obesity, measured by WHR or waist circumference, compared to men, as well as a higher percentage of low HDL-C. Differences by gender for the prevalence of metabolic syndrome were also evident in different ethnic-based studies.[23,29,30] The high prevalence of low HDL-C and obesity, as seen in our women, has also been reported among Indian women and other South Asian women.[4,16,17] This may indicate similar lifestyle factors, such as food habits and less physical activity, which may have influenced the outcome in the women subjects of Indian subcontinent.

The inclusion of similar criteria in both definitions showed a fairly good agreement between the two definitions of metabolic syndrome, with a kappa value of 0.67. Because IDF criteria have the mandatory inclusion of central obesity as compared to any three criteria of the modified ATP III criteria, all of those having metabolic syndrome according to IDF criteria were included in the modified ATP III criteria. On the basis of the observations of the present study and those from other investigators, it is suggested that inclusion of modified waist circumference and BMI cut offs as done in the modified ATP III criteria and IDF definition would probably help identify metabolic syndrome at an earlier stage.

Despite the debate regarding metabolic syndrome as a clinical entity in recent scientific communications, it is clear that definition of the syndrome has relevance only if it identifies individuals at risk both for T2DM and CVD. Thus, the significance of metabolic syndrome should be appraised in relation to its appropriateness for the identification of the individuals at risk. Our study showed that the prevalence of diabetes was 9.4%, whereas 5.6% had impaired fasting glucose (abnormal glucose tolerance 15%). The National Diabetes Survey of Pakistan, using study protocols and standardized World Health Organization (WHO) definitions showed the overall glucose intolerance (diabetes and impaired glucose tolerance [IGT] combined) was present in 22–25% of the subjects, whereas the overall prevalence of IGT in these surveys ranged from 5.39% to 11.2%.[31–33]

Our study showed an alarming prevalence of 49% of the metabolic syndrome in an urban Pakistani population according to the modified ATP III criteria, whereas hospital-based studies have shown a prevalence of 44% using the original ATP III criteria. Our study is probably the first community-based study in an urban population on metabolic syndrome with modified ATP III definitions of metabolic syndrome.

We observed a high rate of metabolic syndrome in the urban population of Lyari Town in the city of Karachi. Its residents comprise a diverse community including every major ethnic group found in Pakistan. Furthermore, the residents also have a mixed socioeconomic personal history. This may help to comprehend the spectrum of the metabolic syndrome in the general population. However, there are some limitations to this study. Despite the use of computerized random selection of households by GIS to minimize the selection bias, the sample size is small. It cannot be generalized for the Pakistani population as a whole, and thus the results have to be interpreted with caution.

Our study may suggest that the burden of noncommunicable diseases such as CVDs and diabetes in our region will be increased as a consequence of higher rate of metabolic syndrome seen in this population. Every effort should be made for the management of the metabolic syndrome to reduce the risks of diabetes and CVDs in this population. This is important, particularly at a time when the global epidemic of metabolic and vascular disease is emerging as a significant public health challenge, with its consequences for diabetes and CVD.

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Dietary Patterns Associated with Risk for Metabolic Syndrome in Urban Community of Karachi Defined by Cluster Analysis

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Abstract: Dietary trends have been found to be related with metabolic syndrome in various studies. To identify dietary patterns and study associations between the dietary patterns of subjects with high and low risk of metabolic syndrome in a Karachi based community. A group of 871 men and women were selected randomly from 532 households. Data about consumption of specific foods was available for 867 adults. Participants completed a health and lifestyle questionnaire and 363 subjects provided fasting blood samples for glucose and lipids. Dietary intake was assessed by a questionnaire to identify consumption of 33 specific food items and the dietary patterns categorized into 6 food groups was assessed by cluster analysis. Five dietary patterns were identified through cluster analysis. Cluster 1 had the lowest proportion of persons with metabolic syndrome i.e. 42.7% while cluster 2 had the highest percentage of metabolic syndrome subjects (56.3%) (p = 0.09). Consumption of fat and caloric dense foods was significantly higher among highest risk group (cluster 2) compared to lowest risk group (cluster 1) (p = 0.0001). The consumption of food groups containing fruit, milk and meat was also more than twice in high risk compared to low risk group (p = 0.0001). Even within the same population there are marked differences in dietary patterns and these apparently contribute to the risk of developing metabolic syndrome. Dietary pattern studies will help elucidate links between diet and disease and contribute to developing healthy eating guidelines.

Key words: Dietary patterns, cluster analysis, metabolic syndrome, South Asians

INTRODUCTION

High prevalence of metabolic syndrome and Cardiovascular Disease (CVD) risk factors have been reported worldwide especially in South Asians (Ramachandran *et al*., 2003; Wierzbicki *et al*., 2005; Basit *et al*., 2002; Jafar *et al*., 2005). Metabolic Syndrome (MS) has been shown to be a good marker of future disease risk and it is estimated that subjects with metabolic syndrome are three times more likely to have and twice as likely to die from a heart attack or stroke compared to people without the syndrome (Sarkar *et al*., 2006). Similarly, people with metabolic syndrome have a five-fold increased risk of developing type 2 diabetes. Although dietary intake has been linked to individual components of MS or the outcome diseases such as diabetes and cardiovascular diseases, the dietary patterns which may lead to the development of metabolic syndrome have not been specified. In recent years there has been increasing interest in the identification of dietary patterns as consumed by populations to better understand the association of diet with chronic diseases (Schwerin *et al*., 1982; Randall *et al*., 1990). During the last two decades, there has been significant changes in society's life style habits with increase in unhealthy eating, sedentary activities and smoking (Panagiotakos *et al*., 2003). These habits have fueled the epidemic of obesity, which is an important risk factor for diabetes, cardiovascular diseases, hypertension and dyslipidemia all of which may be preceded by metabolic syndrome (Basit and Shera, 2008).

The 1990-1994 National Health Survey of Pakistan showed that overall 25% of the population was overweight or obese. The factors significantly associated with obesity were increasing age, being female, higher education, urban residence, high economic status and a high intake of meat (Jafar *et al*., 2006). Knowledge of specific food patterns is important for relating diet to nutritional status and for the identification of groups at risk of under-or over consumption of specific food items (Tucker *et al*., 1992).

Several studies have shown that adopting a dietary pattern characterized by high intake of red meat, refined grains, snacks, sweets and fried foods contribute to the

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increased prevalence of type 2 diabetes (Song *et al*., 2004; Schulze *et al*., 2003; Van *et al*., 2002). Whilst adopting a dietary pattern characterized by high consumption of non-refined cereals, fruits and vegetables, a moderate intake of dairy products, poultry and fish and a low intake of red meat contribute towards a reduced prevalence of type 2 diabetes, metabolic syndrome and cardiovascular disease (Kris-Etherton *et al*., 2001; Trichopoulou *et al*., 2003; Chrysohoou *et al*., 2004).

Thus understanding the food patterns around which diets are formed is important for meal planning and nutritional counseling. Cross-sectionally, dietary intake rich in whole-grain foods have been linked to a lower prevalence of metabolic syndrome (Sahyoun *et al*., 2006; McKeown *et al*., 2004; Esmaillzadeh *et al*., 2005). Dairy intake has been inversely associated with metabolic syndrome (Azadbakht *et al*., 2005; Mennen *et al*., 2000; Pereira *et al*., 2002). Greater intakes of fruit and vegetables have been associated with a lower prevalence of metabolic syndrome (Esmaillzadeh *et al*., 2006). No association has been found between metabolic syndrome and intakes of meat and fish (Mennen *et al*., 2000).

In cross-sectional dietary pattern analysis, a greater prevalence of MS was found among consumers of empty calorie dietary patterns, whereas a lower prevalence was found among those consuming a healthy dietary pattern (Esmaillzadeh *et al*., 2007; Sonnenberg *et al*., 2005).

There are no clear recommendations regarding dietary guidelines for the prevention of metabolic syndrome in persons at risk. The present study will help to evaluate the relationship between dietary intake and the risk of developing MS. Cluster analysis offers advantages over the alternative quantitative approaches as it aims to identify distinct, relatively homogeneous groups based upon selected attributes (the dietary variables) (Hu, 2002).

The aim of the present study is to identify dietary patterns within a general population sample of urban Pakistani subjects. We also aim to report the associations between dietary patterns and prevalence of metabolic syndrome which is a precursor for the development of Cardiovascular Disease (CVD) and glucose intolerance.

MATERIALS AND METHODS

The survey was conducted from July 2004 to December 2004 over a period of 6 months. The Lyari Town Geographical Information System (GIS) was used in this survey which ascribed unique identification numbers to 85,520 households in Lyari, where the study on prevalence of metabolic syndrome amongst selected households was undertaken (Hydrie *et al*., 2009). The ethical approval for the Lyari survey was given by the Institutional Review Board (IRB) of Baqai Institute of Diabetology and Endocrinology. The survey activities were divided into two phases, the household interview based on questionnaire and blood sample collection. The questionnaire included demographical details, diet and physical activity questions and anthropometric measurements.

Around 532 households were randomly selected through the GIS software and maps. All adults older than 25 years were invited to participate after providing signed consent. By following this procedure, a total of 871 persons were approached, out of which 867 persons participated in the survey (response rate: 99.5%). These people were interviewed by the field teams and their anthropometric measures taken. Of these, 363 persons gave blood samples, producing a response rate of 42% for blood collection.

Anthropometry: Weight, height, waist, and hip circumference were measured with the subjects in standing position wearing light clothes and no shoes. The weight was taken to the nearest 0.1 kg by a digital bathroom scale and height was taken to the 0.1 cm. Body Mass Index (BMI) was calculated as a ratio of weight (kg) to height in meters squared. Waist circumference was measured at the minimum circumference between the lower border of the ribs and iliac crest on the midaxillary line and hip circumference was measured at the greatest protrusion of the buttocks just below the iliac crest The measurements were taken in centimeters and the Waist-to-Hip Ratio (WHR) was calculated as waist/hip circumference. Blood pressure was measured twice by using a mercury sphygmomanometer, with individuals requested to sit for 10 min before measuring the blood pressure as a special precaution to minimize blood pressure variations and a mean value taken for the final measurements.

Laboratory assays: All subjects were asked to undertake an 8 h fast for blood tests (fasting blood glucose and lipid profile) that were collected at home on weekends (Hydrie *et al*., 2009). All selected parameters of blood lipids (total cholesterol, triglycerides, High Density Lipoprotein Cholesterol [HDL-C] and Low-Density Cholesterol [LDL-C]) and blood glucose estimation were performed using a Vitalab Selectra autoanalyzer. Fasting blood glucose and lipid profiles were done by the glucose oxidase GOD PAP method and cholesterol CHOD PAP method, respectively.

Criteria for metabolic syndrome: Diagnostic criteria for the metabolic syndrome were taken from the American Heart Association (AHA)/National Heart, Lung and Blood Institute (NHLBI) (Table 1) (Grundy *et al*., 2005).

Table 1: AHA/NHLBI diagnostic criteria for metabolic syndrome

Measure (any three of the five criteria below constitute a diagnosis of metabolic syndrome)	Categorical cut points
Elevated waist circumference	U.S. population: ≥102 cm in men, ≥88 cm in women; lower cut points for insulin-resistant individuals or ethnic groups. For South Asians: ≥90 cm in men, ≥80 cm in women
Elevated triglycerides	≥150 mg/dl (1.7 mmol/l) or on drug treatment for elevated triglycerides
Reduced HDL cholesterol	<40 mg/dl (1.03 mmol/l) in men, <50 mg/dl (1.29 mmol/l) in women
Elevated blood pressure	≥130 mmHg systolic blood pressure or ≥85 mmHg diastolic blood pressure or on drug treatment for hypertension
Raised fasting glucose	Fasting plasma glucose ≥100 mg/dl (5.6 mmol/l) or previously diagnosed type 2 diabetes

Dietary data: Dietary consumption was assessed by a 33 food items interviewer-administered semi quantitative food-frequency questionnaire. The food items were categorized into 6 major food groups: Dairy, meat, fat and sweet, cereals, vegetables and fruits groups. Out of the 363 subjects assessed for metabolic syndrome 362 completed the food-frequency questionnaire.

Statistical analysis: We used cluster analysis to identify dietary patterns and to segregate subjects based on the similarity of diet. We chose food variables because we wanted to identify food patterns clusters. K-means cluster analysis was used to define clusters of subjects using the cluster analysis option in SPSS. This procedure attempts to identify relatively homogeneous groups of cases based on selected characteristics.

In K-means cluster analysis, the homogeneity of cases within a cluster is measured by the total within-cluster sum of squares. Cluster memberships are determined by sequentially moving cases from one cluster to another so that the total within-cluster sum of squares is minimized.

The algorithm requires the number of clusters to be specified prior to analysis. It is possible to identify seeds using information derived from previous research.

Five clusters were defined. We investigated metabolic syndrome prevalence for each cluster and compared the dietary patterns of the clusters with the lowest and highest prevalence of metabolic syndrome.

RESULTS

We identified five distinct groups in this population on the basis of cluster analyses. A total of 75 participants (20.7%) were in cluster 1, 71 (19.6%) in cluster 2, 64 (17.8%) in cluster 3, 85 (23.5%) in cluster 4 and 67 (18.5%) in cluster 5. Frequency of consumption of each food group in all the clusters is shown in Table 2.

Analyzing for proportion of subjects with metabolic syndrome in each cluster it was observed that cluster 1 had the lowest proportion of persons with metabolic syndrome while cluster 2 had the highest percentage of metabolic syndrome subjects (42.7% vs. 56.3%) with a p value of 0.09 compared to the other clusters as shown in Fig. 1.

Table 2: Frequency of consumption of food groups in clusters (%)

	Clusters				
	1	2	3	4	5
Milk group	24	69	32	57	29
Meat group	35	79	61	61	56
Fat group	13	70	20	42	44
Cereal group	76	91	90	92	81
Vegetables group	72	94	83	93	82
Fruit group	34	74	45	59	46

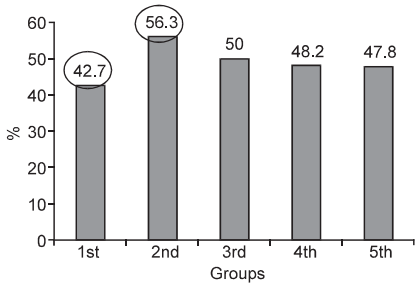

Fig. 1: Metabolic syndrome in five clusters according to modified ATP III definition

Comparing the food items in milk group it was observed that the consumption in cluster 2 (high risk group) was twice compared to cluster 1 (low risk group), the greatest consumption was in cream\custard (7.6 times) and ice cream\sweet lassi (5 times) as shown in Fig. 2.

In meat group the consumption of red meat, organ meat, prawns and eggs in cluster 2 was 3-5 times compared to cluster 1 as shown in Fig. 3.

There was five times increased consumption of the sweet and fat group in cluster 2 compared to cluster 1 as shown in Fig. 4.

In the cereal group there was not much difference in the consumption of legumes and fried rice in both the clusters but around 1.6 times more consumption of naans (refined grain) was seen in cluster 2 compared to cluster 1 (Fig. 5).

In the vegetable group there was also not much difference in the consumption of cooked vegetables and

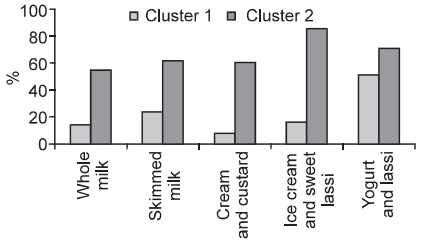

Fig. 2: Comparison of groups with regards to milk group

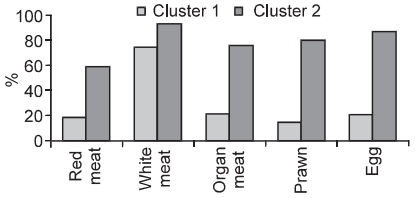

Fig. 3: Comparison of groups with regards to meat group

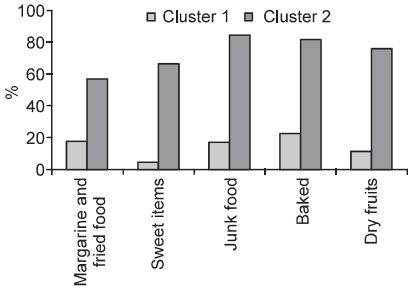

Fig. 4: Comparison of groups with regards to fat and sweet group

cooked potatoes in both clusters but the consumption of raw vegetables was almost double in cluster 2 compared to cluster 1 (Fig. 6).

In the fruit group both clusters showed high consumption of fruits but 8 times more consumption of fruit juices was seen in cluster 2 compared to cluster 1 as shown in Fig. 7.

DISCUSSION

Metabolic Syndrome (MS) has been identified as a precursor of predicting future disease and understanding how MS can be influenced by overall dietary pattern as an entity is valuable.

No individual dietary component is wholly responsible for the association of diet with metabolic syndrome and

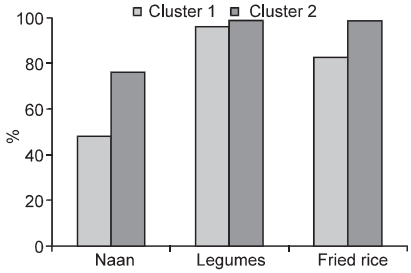

Fig. 5: Comparison of groups with regards to cereal group

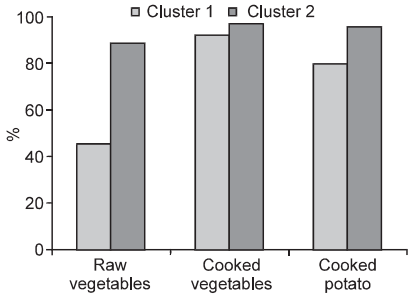

Fig. 6: Comparison of groups with regards to vegetable group

Fig. 7: Comparison of groups with regards to fruit group

its components. Rather it is the interaction between different components of diet as well as the consumption of different food items which contribute to the risk for metabolic syndrome. Thus overall dietary trends needs to be observed as individuals consume a mixture of different food items in a single meal, rather than isolated groups.

To our knowledge, this is the first investigation to look into major dietary patterns and its association with the metabolic syndrome by cluster analysis.

In this study low MS risk group (cluster 1) had lowest consumption of all the food groups while the high MS risk group (cluster 2) had highest consumption in most of the food groups. This high food consumption may also contribute to the high prevalence of MS as seen in cluster 2.

Looking at the food groups individually it appears that the food items which were the most energy-dense had the highest consumption in cluster 2 and this probably had the most influence in creating an unhealthy dietary pattern which may lead to increased prevalence of MS.

It has been observed in other studies that the consumption of traditional food (low in saturated fat, low in simple sugars and high in fibre) has declined recently and energy-dense food (high in calories, carbohydrates and saturated fats and low in fibre) and non-traditional energy-dense fast food are being increasingly consumed in South Asia (Misra *et al*., 2009; Misra and Khurana, 2008).

Studies have shown that South Asians have a high consumption of dairy products and sugar compared to other populations (Misra *et al*., 2009; Popkin, 2001). Although dairy consumption has been inversely related to MS in some studies (Azadbakht *et al*., 2005; Mennen *et al*., 2000; Pereira *et al*., 2002) more than twice dairy consumption was seen in the high risk group. Looking further at the individual food items in the milk group it was observed that the highest consumption was in cream\custard and ice cream\sweet lassi; items which have a high fat and sugar content. Coincidently a high intake of fat, milk products and sugars in various regions in India has also shown to be associated with increased cardiovascular mortality (Gupta *et al*., 2006). Thus a combination of dairy products, with high fat and sugars may influence the individual properties of the food and produce a positive association with metabolic syndrome. In our study these factors probably made dairy consumption lose its protective effect in our subjects as documented elsewhere.

Red meat, organ meat and prawns from the meat group were consumed 3-5 times more in cluster 2 compared to cluster 1. All of these food items are known to be high in saturated fat, which has been adversely associated with cholesterol (Schaefer, 2002), blood pressure (Appel *et al*., 2006), obesity and diabetes risk (Parillo and Riccardi, 2004).

Similarly all the food items in fat and sweet group were consumed five times more in cluster 2 compared to cluster 1. Sweet products were consumed at an alarming 13 times more in cluster 2 and they probably influenced the increased prevalence of MS in cluster 2 with their load of empty calories in the diet.

South Asians consume more carbohydrates compared to Europeans and this may lead to hyperinsulinemia, postprandial hyperglycemia, hypertriglyceridemia and low HDL cholesterol levels, all of which is probably due to insulin resistance (Burden *et al*., 1994). Processed cereals, such as refined grains have been shown to be associated with an increased risk of the components of the metabolic syndrome in The Malmö Diet and Cancer Study (Wirfalt *et al*., 2001). Similarly in our study refined grains were consumed nearly twice in the high MS risk group (cluster 2).

Almost double consumption of raw vegetables was seen in cluster 2 compared to cluster 1. Similarly the overall double consumption of the fruit group was seen in cluster 2. An inverse association between prevalent MS and intakes of fruit and vegetables has been reported previously (Esmaillzadeh *et al*., 2006). Also consumption of diets high in fruit and vegetables has been associated with lower blood pressure (Appel *et al*., 2006) and a better lipid profile (Lichtenstein *et al*., 2006). Looking at the individual food items in the fruit group it was observed that the consumption of fruit juices which accounts to empty calories was 8 times more in cluster 2 compared to cluster 1. As mentioned earlier empty calories in diet may lead to increased prevalence of MS; the increased consumption of fruit juices probably undermined the protective effect which vegetables and fruits may have in cluster 2.

In summary the dietary pattern in cluster 2 was loaded with both healthy (milk, legumes, vegetables and fruits) and unhealthy (refined grains, potatoes, meat and meat products, high fat dairy products, snacks, sweet items and fruit juices) foods. Although the healthy foods have been reported to be protective against the metabolic syndrome, the cluster's unhealthy diet constituents have adverse effects on metabolic markers which may lead to increased prevalence of MS.

A limitation to consider in the interpretation of our results is the use of an FFQ containing only 33 items, thus restricting the number of food items needed to characterize usual dietary intake. Furthermore, for some food groups such as dry fruits, low consumption and a narrow range of values among consumers may have prevented us from detecting a relationship if one was present. Moreover, reporting biases may have occurred. Although we acknowledge these limitations, other studies have indicated that there is reasonable validity and reliability of food groups and major dietary patterns obtained from FFQs.

Another limitation of our study is its cross-sectional nature. Thus, the association observed between these dietary patterns and the metabolic syndrome needs to be confirmed in prospective analyses. Furthermore we cannot generalize our findings to Pakistani populations, since only one area within an urban city was used for the sample population.

However, participants in the current study reflected almost all major ethnic groups of Pakistan so that a broad range of dietary habits were represented. Most previous studies relating MS to diet have focused on a

single food group. Thus, a major strength of our study is that all six major food groups have been covered in the FFQ.

Thus we need to further explore the development of a method which accurately measures an individual's overall diet quality and quantity and this is a prerequisite for further research regarding the relationship between diet and metabolic syndrome. Further research is required in larger prospective populations to be able to validate the findings of this study and improve our understanding of the association of diet with MS.

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Title:

Detecting Insulin Resistance in Pakistani Subjects by Fasting Blood Samples

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ABSTRACT:

Background
Insulin Resistance has been identified as an independent risk factor for a number of chronic diseases such as diabetes and cardiovascular diseases (CVD).
Objective
To identify a simple indirect method for detecting insulin resistance (IR) in our population.
Methods:
Geographical Imaging Systems (GIS) was used for randomly selecting the subjects. For visiting the 532 households selected by GIS, 9 field teams were developed. A total of 871 subjects older than 25 years were approached by these teams out of which 867 agreed to participate in the survey. IR was assessed in 227 normal subjects by fasting insulin, HOMA-IR, QUICKI and McAuley Index.
Results:
IR was defined at 75th percentile cut off of insulin levels (9.25 U/mL) and HOMA-IR (1.82). The 25th percentile cut off was used for defining IR in QUICKI (0.347) and McAuley Index (6.77).
Conclusion:
A common approach towards managing subjects with metabolic risk factors will help identify IR earlier and using IR reference values identified from simple indirect methods would be of value in such cases. However larger population based studies are needed to further define and validate these cutoff values for insulin resistance.
Key words: Insulin Resistance, Fasting Blood Levels, Metabolic Syndrome, Pakistani, HOMA, QUICKI, McAuley Index

INTRODUCTION
Insulin Resistance (IR) is an acronym for a wide range of metabolic derangements with convincing evidence that it is an independent risk factor for a number of chronic diseases such as diabetes and cardiovascular diseases (CVD). Insulin resistance has also been suggested as the primary cause leading to the clustering of risk factors such as glucose intolerance, hypertension, elevated serum triglycerides, low serum HDL cholesterol and central obesity which together have been labeled as Metabolic syndrome (MS) (1).
Elevated insulin levels are believed to accelerate the development of atherosclerosis and is considered to be a key cause of cardiovascular pathologies in metabolic syndrome (2-3). High death rates from coronary heart diseases have been associated with insulin resistance and metabolic syndrome (4). It has also been observed that reduction in insulin resistance improves glycaemic control and favourably modifies other components of the metabolic syndrome (5). Thus diagnosis of insulin resistance at the initial stages of a disease could be used as a effective measure to prevent unfavourable outcome, including reduction of cardiovascular morbidity and mortality.
Unfortunately reliable methods for measuring insulin resistance in vivo such as the hyper-insulinemic euglycemic clamp and minimal-model approximation of the metabolism of glucose (MMAMG) are time-consuming, complicated and require expensive equipment for epidemiological research as well as for clinical practice (6 -8).
For this purpose insulin resistance indices have been developed based on fasting blood samples (serum insulin and glucose levels) which are used as reference cutoffs defined for various populations (9). The homeostasis model for insulin resistance (HOMA-IR), the quantitative insulin sensitivity check index (QUICKI) and McAuley Index are commonly used surrogate measures from these fasting values and have proven to be a reliable alternative

to the glucose clamp studies (8, 10-11). Many studies using these simple indirect methods for detecting insulin resistance have been reported (12-14).
Studies done in Pakistani population comparing hypertensive subjects with normal subjects, showed high levels of insulin in hypertensive subjects ($p<0.001$), likewise children having family history of cardiovascular disease had higher insulin levels compared to children with family history of diabetes, while fasting insulin and cholesterol levels was significantly higher in diabetic subjects compared to controls in another Pakistani study with a p value of <0.01. (15-17).
Although the prevalence of metabolic syndrome has been reported in Pakistani population, no population based study measuring insulin resistance in Pakistani adults have been reported to our knowledge (18-20). Because of the lack of information on insulin resistance in our local population we decided to determine the reference cut off values of IR indices from our community based epidemiological study done previously (20).

MATERIALS AND METHODS

Study area and population

The survey was conducted from July 2004 to December 2004. Geographical Imaging Systems (GIS) was developed for Lyari Town with unique identification numbers ascribed to households and the prevalence of metabolic syndrome was studied by random selection of these households (20).

Methodology

The ethical approval for this survey was given by Institutional Review Board (IRB) of Baqai Institute of Diabetology and Endocrinology. The survey activities were divided into two phases - the household interview plus physical examination and blood sample collection, both have been described in detail previously (20). Nine field teams visited the 532 households which were selected by GIS and approached a total of 871 subjects > 25 years of age out of which 867 agreed to participate in the survey. Anthropometric and demographic information was collected during the interview. Waist and hip circumference was measured and blood pressure taken twice by using mercury sphygmomanometer.

Laboratory assays

All adults > 25 years were asked to undertake a 10 hours fast for blood tests (fasting blood glucose, lipid profile and insulin levels) for which blood samples were collected on weekends. Blood samples were given by 363 persons out of the 867 adults who took part in the survey. All selected parameters of blood lipids (total cholesterol, triglycerides, HDL- cholesterol and LDL-Cholesterol) and blood glucose estimation was done using auto-analyzer Vitalab Selectra. Fasting blood glucose and lipid profile were done by GOD PAP method and CHOD PAP method respectively.

Insulin

Fasting insulin was measured by enzyme linked immunosorbent assay (ELISA) based on the sandwich principle. The specificity of antibodies or cross reactivity of the kit to the proinsulin was zero percent. The analytical sensitivity of the assay was found to be 1.76 uIU/ml.

Assessing insulin resistance

Insulin resistance was assessed in 227 normal subjects by calculating HOMA, QUICKI and McAuley Index indices as follows:
HOMA-R = Insulin (Iu/ml) × glucose (mmol/l)/22.5
QUICKI = 1/ [log (fasting insulin) + log (fasting glucose)]
McAuley Index = Exp [2.63-028 ln (Insulin in Mu/l)-0.31ln (triglyceride in mmol/l)

STATISTICAL ANALYSIS

Characteristics of the subjects according to gender were analyzed using an independent sample t-test. Data was presented as quartiles of fasting insulin, HOMA-IR, QUICKI and McAuley index to observe the various percentiles of insulin sensitivity and determine insulin resistance according to defined standard protocols.

The statistical analysis was conducted using SPSS for Windows (version13, SPSS Inc., Chicago, IL, U.S.A.), and $p<0.05$ was considered statistically significant.

RESULTS

Subjects with fasting blood sugars $\leq$ 100 mg/dl were taken as having normal glucose tolerance. A total of 227 normoglycemic subjects (70 men and 157 women) were selected from the survey population.

General characteristics of the study participants are shown in Table 1. Females were significantly younger than males with lower waist circumference but higher Body Mass Index (BMI). Mean total cholesterol and LDL cholesterol was higher in females compared to males. Mean fasting insulin and HOMA-IR was also higher in females while other indices of insulin resistance were not much different in males and females. Males had significantly higher blood pressure compared to females.

The 75^{th} percentile cut off was used as a value for defining insulin resistance for fasting insulin levels (9.25 U/mL) and for HOMA-IR (1.82) while the 25^{th} percentile was taken as cut off for defining insulin resistance according to QUICKI (0.347) and for McAuley Index (6.77) as shown in Table 2.

DISCUSSION

In this study females had higher fasting insulin levels compared to males; internationally there are contrasting studies about gender based insulin differences with some showing higher insulin resistance in one gender compared to the other (21).

Researchers have suggested that a fasting insulin level at 75^{th} percentile cutoff is accurate at predicting insulin resistance in normal non diabetic population in some studies (4,9). Fasting insulin levels at 75th percentile was thus used as a cut off value in this study and this value lies within the range observed in other studies (4,9,22).

In 1985 Matthews was one of the pioneers to define HOMA-IR as a simple and reliable method for estimating insulin sensitivity from fasting plasma glucose and insulin levels (11). HOMA-IR values between 1.21 and 1.45 were reported for normal subjects by Matthews (11). Many large population-based studies have used HOMA-IR to assess insulin sensitivity and reported HOMA-IR to be around 2.6 on the basis of the 75th percentile (4,10,13,14). However lower HOMA-IR values have been observed in south asians with an Indian study reporting HOMA-IR to be 1.93 at the 75^{th} percentile while in our study it was observed to be even lower at 1.82 (23).

Other researchers suggested QUICKI to be a better surrogate measure of insulin resistance than HOMA-IR (12). The 25th percentile value of QUICKI was 0.347 in our study which lies within the range reported for normal populations (0.33-0.372) by other researchers (4, 24).

It has been suggested by some that incorporating triglycerides in asian subjects increases the likelihood of identifying insulin resistance (25). The index proposed by McAuley for the diagnosis of insulin resistance incorporates triglycerides in its formula (9). Thus we calculated McAuley index on the basis of the 25th percentile and in our study the cutoff of McAuley index was 6.77. Thus we calculated the cut off values for defining insulin resistance in our population by using simple fasting blood levels of insulin and glucose.

However our study had a few limitations. Firstly, the diagnosis of insulin resistance was based only on a single test of fasting blood glucose and insulin levels. Hyperinsulinemic euglycemic clamp studies were not performed to correlate the findings of indirect methods of insulin resistance with the gold standard test in this case. However, WHO has suggested that the 75th percentile cutoff of insulin can be used for epidemiological studies, which was done in this study (26). Although the sample size was small and generalizing the cutoff values for Pakistani population have to be taken with caution, the randomization of the sample was done by GIS which reduces bias in sample selection. Thirdly, although insulin assays can vary considerably depending on cross-reaction with proinsulin, in this study human insulin-specific radioimmunoassay was used which has no significant cross-reactivity with proinsulin thereby minimizing the interference by proinsulin (27).

Determining cutoff values of IR by indirect measures could help in identifying insulin resistant subjects in clinical practice on account of their simplicity and clinicians may be able to use this simple test as an initial screening tool to identify such subjects. Thus clinicians may intervene earlier in insulin resistant subjects to prevent the development of type 2 diabetes, hypertension and cardiovascular diseases in such subjects. However since the values are not universally applicable because of the variability of values studied in different populations we need to have specific population based studies and this was such an attempt in the Pakistani population. Studies have shown that when compared with the insulin sensitivity value obtained by the MMAMG method the sensitivity of McAuley was observed to be significantly higher than that of HOMA-IR or QUICKI (4,9). However HOMA-IR has been most widely studied as an indirect method for IR and has been considered by many researchers to be a good measure of IR (4,7).

Although determining insulin resistance by indirect methods is difficult due to the variability of results, but the cut off values of IR determined can be used as a measure of insulin resistance in Pakistani adults.

It is hoped that a common approach towards managing subjects with metabolic risk factors by using a single cutoff value will help save time and improve clinical assessment by identifying such cases of insulin resistance earlier. Secondly the clinical focus may shift from identifying the various risk factors separately towards identifying insulin resistance by using reference values measured from these simple indirect methods.

However larger population based studies are needed to further define and validate these cutoff values for insulin resistance in this south asian population.

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Table 1: General characteristics of the study subjects

Subject	Male Mean ± SD n = (70)	Female Mean ± SD n = (157)	P value	Total Mean ± SD n = (227)
Age (yr)*	43.10 ± 12.95	36.87 ± 11.40	**< 0.000**	38.79 ± 12.21
Body Mass Index (kg/m^2) **	22.35 ± 4.10	25.09 ± 6.27	**0.002**	24.27 ± 6.07
Waist Circumference (cm)	87.42 ± 12.84	85.31 ± 14.09	0.288	85.96 ± 13.72
Systolic Blood Pressure (mmHg)	127.94 ± 19.95	121.73 ± 17.14	**0.033**	123.59 ± 19.55
Diastolic Blood Pressure (mmHG)*	84.70 ± 12.11	77.70 ± 12.87	**< 0.000**	79.79 ± 13.02
Cholesterol (mM/L)	175.06 ± 44.02	178.72 ± 44.85	0.581	177.61 ± 44.53
Triglyceride (mM/L)***	160.58 ± 123.27	128.90 ± 66.33	**0.018**	138.39 ± 88.25
Low Density Lipoprotein (mM/L)	108.22 ± 30.15	114.48 ± 32.56	0.181	112.59 ± 31.91
High Density Lipoprotein (mM/L)***	38.65 ± 11.52	43.48 ± 12.52	**0.009**	42.04 ± 12.40
Glucose (mM/L)	80.80 ± 8.82	79.94 ± 10.63	0.556	80.21 ± 10.10
Insulin (μU/mL)	7.60 ± 2.78	8.40 ± 4.50	0.178	8.15 ± 4.05
HOMA	1.48 ± 0.58	1.61 ± 0.90	0.258	1.57 ± 0.81
QUICKI	0.36 ± 0.02	0.36 ± 0.03	0.889	0.36 ± 0.03
McAuley	7.09 ± 1.33	7.37 ± 1.48	0.138	7.29 ± 1.44

* P-value < 0.001 ** P-value < 0.005 *** P-value < 0.05

Table 2: Quartiles of fasting serum insulin, HOMA-IR, QUICKI and McAuley Index.

	P25	**P50**	**P75**
Insulin	5.95	7.8	9.25
HOMA-IR	1.087	1.454	1.823
QUICKI	0.347	0.359	0.376
McAuley Index	6.77	7.046	7.33

Effect of intervention in subjects with high risk of Diabetes Mellitus in Pakistan.

Running title:

Effect of intervention in high risk subjects of DM in Pakistan

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Abstract:

Aims: The aim of the study was to observe the rate of conversion from impaired glucose tolerance (IGT) to diabetes following lifestyle modification program and a combination of lifestyle modification and oral hypoglycaemic agent (metformin) compared to a control population with 18 months follow up.

Methods: Around 40 screening camps were organized at places such as organizations, factories and health care centre. Nearly 5000 people attended lectures and visited the screening camps. Of these 2300 filled a high risk questionairre and 1825 subjects over 30 years of age were identified as high risk. They were requested to undertake an oral glucose tolerance test (OGTT). Out of these 1739 subjects took the OGTT and 317 subjects were identified as having impaired glucose tolerance (IGT). They were randomized into three groups. First group was given standard medical advice (Control Group), second group was given intensive lifestyle modification advice (LSM Group) while third group was given intensive lifestyle modification advice and metformin 500mg twice daily (LSM+Drug Group).

Results: At the end of the study 273 subjects completed the study giving a compliance rate of 86%. A total of 47 incident cases of diabetes were diagnosed during the study. The overall incidence of diabetes was 4 cases per 1000 person-months with the incidence of diabetes as 8.6 cases in the control group, 2.5 cases in the Life Style Modification (LSM) group and 2.3 cases in the LSM+drug group.

Conclusions This study showed that lifestyle intervention had a major impact in preventing diabetes among IGT subjects in this region. However, addition of drug in the intervention did not show any improved results. Resource constrain societies are challenged with the additional burden of diabetes cost on their already ailing economy. Therefore, we recommend that lifestyle modification advice and follow-up should be incorporated in primary health care.

Keywords: IGT, primary prevention, diabetes, lifestyle intervention, metformin.

Introduction:
The prevalence of diabetes is increasing globally and the burden of the disease is making it one of the most challenging public health problem of the 21st century with Asia as the epicentre (1;2). It is increasing in epidemic proportions with one person developing diabetes every five seconds globally (1;2). Once diabetes develops it causes disability, increased health costs to the person and reduced life expectancy with somebody dying from diabetes every ten seconds in the world (2). Thus diabetes is a chronic debilitating disease causing life long complications such as heart disease, blindness, kidney damage and foot amputations. The most dramatic increase in type 2 diabetes is occuring in genetically predisposed populations where rapid and major lifestyle changes are taking place. These include changes in diet and reduction in physical activity, with consequent increase in the prevalence of obesity leading to increased burden of diabetes (2;3). Diabetes leads to increased morbidity and mortality, with the only way to reduce this is to prevent it from developing.

Randomized controlled trials have shown that progression to diabetes can be reduced in people at identifiable risk through interventions (2-4). Thus evidence from clinical trials suggest that subjects at risk of developing diabetes can prevent or delay the onset of type 2 diabetes by lifestyle modification or medication (2;3). A number of studies done in China, Finland, USA and India have demonstrated the importance of healthier lifestyle in preventing or reducing the occurrence of diabetes (3;5-9). The collective results of such prevention studies showed an average reduction of 51% in new cases of diabetes (4). Studies from Finland and USA showed that the most powerful way to prevent the occurrence of diabetes was to modify lifestyle condusive to improved metabolic health (6-8).

Most intervention studies targeted diabetes prevention by achieving and maintaining a healthy body weight through a combination of dietary measures and physical activity in high risk subjects (2). However, based on genetics and defining cardio-metabolic state including level of obesity, fat deposition pattern and dietary habits in different populations, this intervention strategy may need to be revised. For example, different ethnic groups have different body mass index (BMI) cutoffs which may have a varied effect on intervention as evident in the Indian study where risk reduction rate of 28% was seen compared to 58% risk reduction of diabetes in the Finnish and USA studies (7-10).

One limitation of the study in India was that the subjects were recruited from the local railway company and most of them were vegeterians. South Asians are a heterogenous group based on different religious and cultural practices including food habits and they are genetically different. Studies have also noted dietary differences within the ethnic groups in South Asians (11;12). For example, the diet of South Asians (mainly Punjabi) studied in Scotland was found to have large differences between Muslim and non-Muslim groups, with Muslims more likely to eat meat and less likely to eat fruit and cooked vegetables than non-Muslims (13). This difference was also seen in another study between Muslims and Hindus (probably due to their vegetarianism) (14). This difference in diet due to ethnicity and religion may have a effect on intervention strategies and needs to be further explored to better understand the effect of intervention programs in these communities.

Therefore we conducted this intervention study in the largest city (Karachi) of Pakistan amongst the general population where most of the people were muslim and non vegeterian. The main aim of the study was to observe the rate of conversion from IGT to diabetes following lifestyle modification program and a combination of lifestyle modification and oral

hypoglycaemic agent (metformin) compared to a control population with 18 months follow up.

Methodology:
Location:
Karachi is the largest and most populous city of Pakistan. All the major ethnic groups of the country are represented here with Muhajirs forming the dominant ethnic group in Karachi. Our primary prevention team visited different primary health care centres within the city to generate awareness and distributed educational leaflets about our primary prevention program.

Study Procedure
A number of strategies starting with opportunistic screening at 2 different out patient clinics was adopted to secure participation of the general population and create awareness about diabetes prevention. With the aim to reach a larger audience our diabetes prevention team arranged a series of 2-days awareness lectures at various places in the city by going to offices, service organizations, factories and visiting health care centres. Lectures on diabetes and its prevention were delivered by the prevention team in local language to the audience on the first day. The audience were asked to fill a risk questionnaire at the end of the first day. On the second day, screening of high risk subjects was done according to results of the questionnaire and all high risk subjects were invited for an OGTT. During the time OGTT was done, all the subjects underwent a detailed anthropometric and medical examination as well as been asked about their socio-demographic, physical activities and dietary habits including information on quantity and quality of meals by a dietician and physical trainer.

Design of the study:
This was a randomized clinical trial (RCT) conducted in subjects over 30 years of age who were diagnosed as having IGT according to World health Organization criteria (15). The IGT subjects were followed for a period of 18 months prospectively.

A questionnaire was filled as the first step to identify subjects from the overall population who may be at an increased risk of developing type 2 diabetes. . This standardized questionnaire included (a) family history (parents or siblings with diabetes), (b) high body mass index, (c) low physical activity, (d) age, (e) hypertension, (f) high cholesterol or triglycerides (g) history of gestational diabetes or birth weight > 3.5 Kgs. Those identified as high risk (n=1825) were requested to undergo an Oral Glucose Tolerance Test (OGTT). Of these 1739 came for the OGTT giving a response rate of 95.3%. Subjects with 2 hour glucose levels between 140 to 199 mg/dl were identified as having impaired glucose tolerance (IGT) and were requested to participate in the study. Those who were diagnosed with diabetes (n=181) were referred to respective hospitals for further medical care.

After taking informed consent, the participants were randomized by age stratas (31- 40 years, 41–50 years, 51–60 years and > 60 years) into three different arms. This was to ensure equal age representation in all the arms of the intervention. The three groups as shown in the flowchart were followed for 18 months (Figure 1). First group was given standard medical advice (Control Group), second group was given intensive lifestyle modification advice (LSM Group) while third group was given intensive lifestyle modification advice and metformin (LSM+Drug Group).

Subjects
An estimated 5000 people attended the diabetes prevention lectures and visited the screening camps. Of these 2300 filled a high risk questionairre and 1825 were identified as high risk subjects which were requested to undertake a standardized oral glucose tolerance test (OGTT). Around 1739 agreed and out of these 317 subjects were identified as having impaired glucose tolerance (IGT group).

Of the 1739 subjects who underwent OGTT, 72% were males, 10.4% were found to have diabetes and 18% were having impaired glucose tolerance (IGT). The baseline characteristics of the 1739 subjects showed an increasing trend in terms of age, BMI, and blood pressure from NGT to DM as shown in table 1 below.

Investigations
All IGT subjects had fasting lipid profile, fasting insulin levels, OGTT and HbA1c done at 0, 9 and 18 months. At the interim 9-month visit, confirmation of diabetes was made with OGTT. Plasma glucose was measured using the glucose oxidase–peroxidase method. The fasting serum lipid profile was estimated using standard enzymatic procedures. HbA1c was measured by HPLC using Biorad, a procedure certified by the National Glycohemoglobin Standardization Program. Weight, height, waist circumference and blood pressure were measured at each scheduled visit. All the subjects in the IGT cohort were seen after the OGTT tests and randomized into one of the three groups at baseline (0 week). They were followed according to their assigned groups and seen every two months by the primary prevention team. At 9 and 18 months blood tests were done to confirm their glucose status and assess their biochemical parameters. Weight and height was measured with the subjects minimally clothed, without shoes, in a standing position. Waist circumference was measured at the mid-point between the iliac crest and the costal arch. Blood pressure was measured twice, 5 min apart, in a sitting position, and the average of the two readings were recorded.

Intervention and Randomization
All subjects who agreed to participate in the study were randomized into three groups as shown in figure 1. The subjects assigned to their respective groups were followed till the end of the study.

Subjects in the intervention group were given detailed advice about how to achieve the intervention goals, which included reduction of ≥ 5 % of body weight loss via diet control and physical exercise, total fat intake less than 30% of energy consumed, fiber intake of 15g/1000 kcal, and moderate exercise for minimum 30 min/day. Frequent ingestion of wholemeal products, vegetables and fruits, low-fat milk and meat products, and vegetable oils rich in monounsaturated fatty acids was recommended. The subjects had sessions with a dietician and physical trainer at each visit and they were individually counselled to increase their level of physical activity. Endurance exercises such as walking, jogging and cycling were recommended to improve fitness. Supervised, individually tailored training advice was also offered to improve the physical fitness of each individual. These interventions were based on reinforcing behaviour modification via diet change and encouraging physical activity in each subject.

Subjects in the control group were given general diet and exercise information at baseline and followed at subsequent visits but no specific individual counselling was done. While subjects in the intervention+drug groups were also seen every 2 months by a medical doctor for their drug adherence.

Follow-up
Reinforcement and counselling was done every 2 months in all groups with the intensive groups seen by the medical officer, dietician and physical trainer, while the control group seen only by the medical officer as described in detail elsewhere (16).

Primary Outcome:
The primary outcome was defined as developing diabetes indicated by either fasting plasma glucose of (> 125 mg\dl) and \or 2-hours plasma glucose of (>199 mg\dl) confirmed at 9 & 18 months follow-up by an OGTT (15). Subjects identified as having diabetes were excluded from the study and given medical advice with referral to physicians for further follow-up.

Ethics
The project was approved by BIDE ethics committee and the Norwegian Research Council. All high risk subjects gave written informed consent at the start of the study. Records were kept for any adverse effects occurring during the course of the study.

Statistics
Mean and standard deviation were reported for continuous variables and inter-group comparisons were tested by two tailed ANOVA. Comparison of proportions was by $\chi 2$ analysis. The proportion of subjects developing diabetes in each group and their comparison was by $\chi 2$ analysis.
For the intervention measures, the absolute and relative risk reductions and 95% CIs of the estimates and the number needed to treat to prevent diabetes in one person were calculated. A p value <0.05 was considered significant. The statistical package SPSS (PASW Statistics 18) was used for analyses.

Results:
The IGT subjects (317) were randomized into three groups as shown in table 2. More than half (56%) of the subjects were between 30-44 years of age in the IGT cohort while 36% of the subjects were unskilled\skilled manual labourers. Positive family history of diabetes, hypertension, cardiovascular disease and stroke was present in 49%, 38%, 31% and 17% of the subjects respectively while 25% had hypertension at the start of the study.

During the course of the study, the mean body weight and waist circumference decreased in the LSM and LSM+Drug groups while it increased in the control group as shown in figure 2 and 3.

At the end of the study 273 subjects completed the study giving a response rate of 86%. A total of 47 incident cases of diabetes were diagnosed during the study; 19 cases at 9 months and 28 cases at 18 months or closure of the study. The overall incidence of diabetes was 4 cases with 8.6 cases in the control group, 2.5 cases in the Life Style Modification (LSM) group and 2.3 cases per 1000 person-months in the LSM+drug group as shown in table 3. The numbers to be treated to prevent one incident case of diabetes was 9 and 8 in lifestyle and LSM+Drug groups respectively.

Adverse Events:
Overall 44 subjects dropped out or were lost to follow up. In the control group there were 2 deaths while 24 subjects dropped out during the study. In the lifestyle modification group 8 subjects refused to continue the study and dropped out. In the LSM+Drug group 5 subjects stopped taking the drug either due to side effects of the drug such as gastrointestinal problems

or complaining of weakness probably due to hypoglycemia while 5 subjects refused to follow due to personal reasons and were lost to follow up.

Discussion:

Our data suggest that lifestyle intervention is highly effective in preventing high risk individuals (IGT) from conversion to diabetes in this population. Adding oral hypoglycaemic agent (metformin) in addition to lifestyle modification was not found to be advantagious for the prevention. Our data is in line with the previous studies done in other population (6-9).

The progression rate of IGT to diabetes in our control subjects was lower compared to Indian and Chinese controls (8.2% per 12 months compared to 18.3% and 11.3% per 12 months respectively) (5;9). But this was significantly higher than seen in the Finnish (6% per year) and DPP (11 per 100 person-years) studies (5;7;8). All subjects in the control group also received general health advice about diet, nutrition and exercise at baseline and at subsequent follow-up visits. This may have helped to increase their awareness about their diabetes risk and some subjects may have benefited from the advice or made subsequent lifestyle modifications due to this. A absolute reduction of 10.7/100 was seen in the intensive lifestyle group, which was greater than seen in IDPP (15.7/100) (9). More number of subjects were needed to treat in order to prevent one case of diabetes in the intensive group (9 vs 6.4) in our study compared to IDPP (9).

Looking at the baseline characteristics it appears that our subjects were similar in age as other Asian studies (Mean age Indian 45.9±5.7 years, Chinese 45±9.1 years and ours 43.6±9.9 years) but had comparatively higher BMI (kg/m2) (Indian 25.8±3.5, Chinese 25.8±3.8 and ours 27.1±5.0) (5;9). However our subjects were still younger and leaner compared to the Finnish (age 55±7.0 years, BMI 31±4.6) and the American subjects (age 50.6±10.7 years, BMI 34±6.7) (6;8). The follow-up period in our study was nearly half in duration (only 18 months) compared to the Indian, American and Finnish studies (6-8).

In our study the progression of IGT to diabetes was comparable to other Asian studies and it showed the effectiveness of lifestyle modification involving moderate physical activity and diet modification to prevent diabetes in this population. Adding metformin had an additional benefit but its impact was quite small with the relative risk reduction of 5.5%, from 71% to 76.5% in the lifestyle modification+drug group. This difference was not found to be statistically significant.

Our results showed that to reduce the burden of diabetes epidemic, effective primary prevention can be achieved through lifestyle modification. Therefore, it is suggested that necessary policy development on the prevention of diabetes should emphasis on the lifestyle modification. Recent Updates from the China DaQing Prevention Study, the Finnish Diabetes Prevention Study, the American Diabetes Prevention Programme Outcome Study and the Look Ahead Study have all shown that the most efficient way to manage diabetes and its complications is to prevent diabetes in the first place. This in turn has lead to policy documents from expert organizations such as The Disease Control Priorities project (DCP-2), the European Society of Cardiology and European Association for the Study of Diabetes, the Canadian Diabetes Association, the American Diabetes Association, and the International Diabetes Federation, all recommending lifestyle changes such as weight loss and increased physical activity for the prevention of T2DM among those with pre-diabetes (2;9;17-21).

The main motivation for the prevention of type 2 diabetes is that it can prevent or delay the onset of diabetes and its complications, thereby reducing the life entrenched financial burden

and unnecessary human sufferings of diabetes on both the individual and on the society at large. Developing countries have to face this additional burden on their already ailing economy (22;23); therefore, primary prevention programmes need to become a integral part of Primary Health Services and strategies for reducing the diabetes burden at all levels.

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FIGURE 1: Flowchart with recruitment of persons for the oral glucose tolerance test (OGTT) and screening and randomisation.

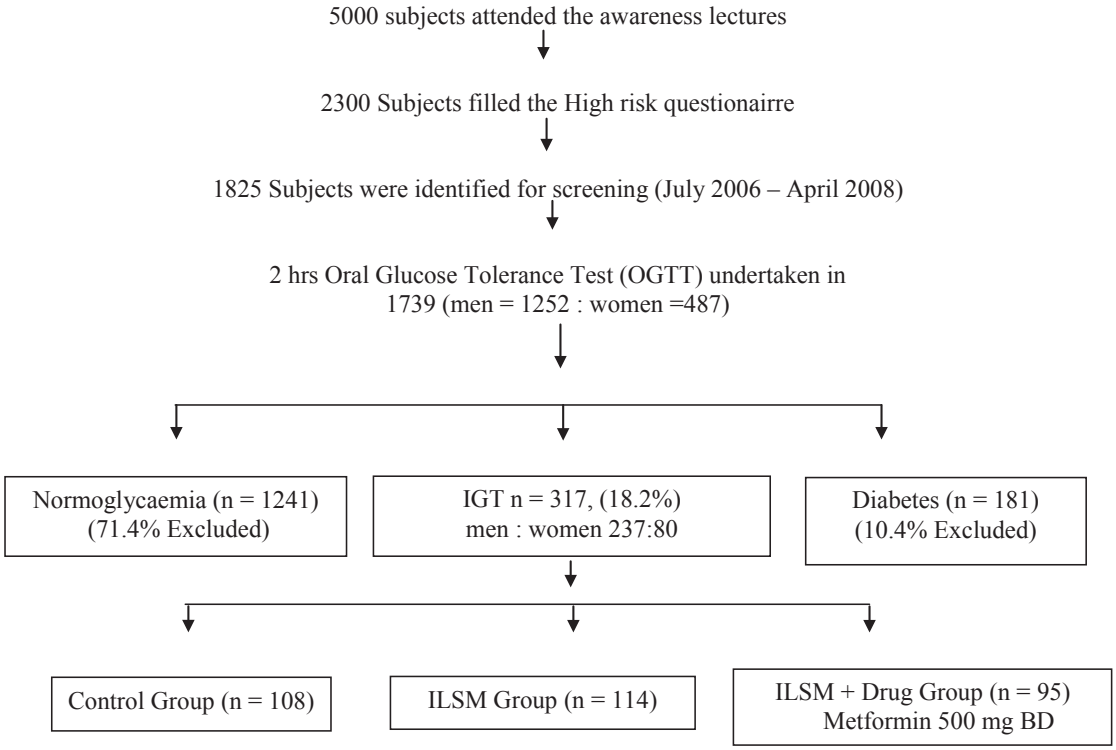
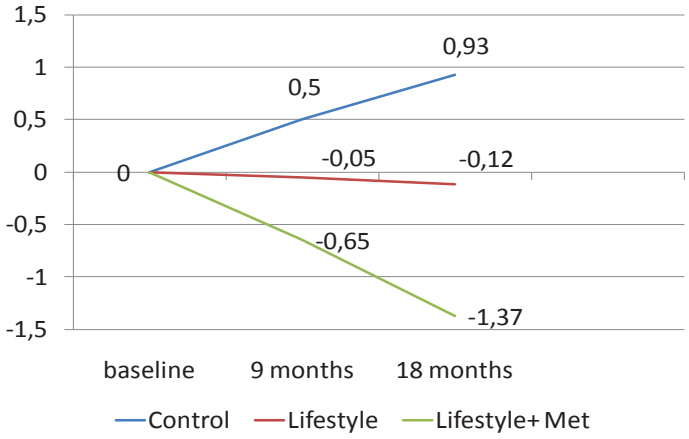


Figure 2: Weight changes in 18 months



(*p value = 0.003)

Figure 3: Waist Circumference

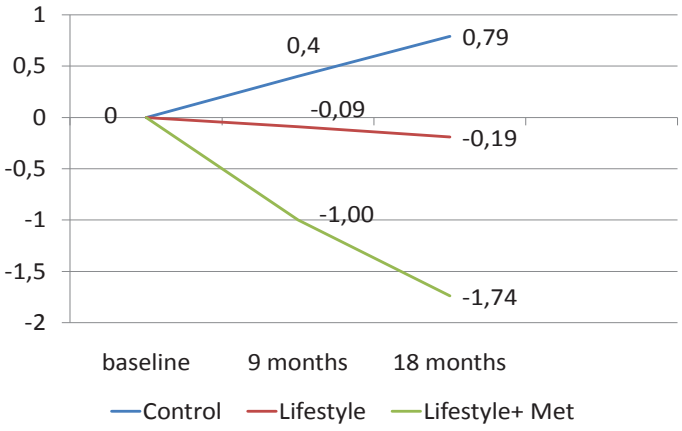


Table 1: Baseline Characterstics of 1739 identified high risk subjects by questionnaire

	NGT	**IGT**	**DM**	**p-value**
N	1241	317	181	
Age of patient (years)	40.1 ± 8.9	43.6 ± 9.9	44.4 ± 9.7	<0.0001
Body Mass Index (kg\m^2)	25.8 ± 5.3	27.1 ± 5.0	27.3 ± 5.2	<0.0001
Systolic BP (mmHg)	118.3 ± 16.5	121.5 ± 16.8	124.3 ± 17.7	<0.0001
Diastolic BP(mmHg)	82.5 ± 11.0	84.6 ± 10.9	85.4 ± 13.1	0,001

Table 2: Baseline Characteristics of the 317 Subjects in the IGT Cohort

	Control	**Lifestyle**	**Lifestyle+ Met**
N	108	114	95
Age in years	44.2 ± 10.9	43.1 ± 10.1	43.5 ± 8.4
Body Mass Index (kg\m^2)	27.0 ± 5.7	26.1 ± 4.7	28.1 ± 4.3
Systolic BP (mmHg)	121 ± 17	123 ± 19	120 ± 14
Diastolic BP(mmHg)	84 ± 11	86 ± 12	84 ± 9
Cholesterol (mg/dl)	179.1 ± 37	178.6 ± 34	180.0 ± 36
Triglycerides (mg/dl)	153.4 ± 109	147.3 ± 86	171.5 ± 119
HDL-C (mg/dl)*	37.8 ± 4.3	37.4 ± 4.5	37.8 ± 7.8
LDL-C (mg/dl)	117.2 ± 25.1	116.5 ± 22.7	117.0 ± 24.6

Table 3: Comparision of the outcome at 18 months in the four groups

	Control	**Lifestyle**	**Lifestyle+ Met**
N	82	107	85
cases per 1000 person-months	8.6	2.5	2.3
Absolute risk reduction %		10.7	11.5
Relative risk reduction % (95% CI)		71(13.7-90.3)	76.5(19.7-93.1)
NNT for 18 months to prevent DM in one case		9	8